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Subtitle: **Thirteen-Week Inhalation Toxicity Study with Aerosol Mixtures of Fog Oil and Graphite Particles in F344/N Male Rats**

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The potential inhalation hazard of obscurant materials to which military personnel may be exposed during field operations was investigated in a 13-week whole-body inhalation toxicity study of mixtures of aerosols of a petroleum-based liquid (PBL) fog oil and a solid particulate (graphite) conducted in male F344/N rats. Exposures were 4 hr/day, 4 days/week to aerosol mixtures of 250, 500 or 1000 mg/m^3 PBL and 100 or 200 mg/m^3 graphite. The low and high PBL concentrations were tested in combination with the low and high graphite concentrations, respectively, while the mid PBL concentration was tested in combination with both graphite concentrations. A fifth group was a filtered air control. Animals were monitored throughout the study for clinical signs, body weight gain and food consumption. Selected biologic end points including pulmonary lavage parameters, pulmonary function, clinical pathology, histopathology, and lung/body weight ratios were evaluated after the last exposure and after a 6-week recovery period. Multivariate and univariate analysis of variance models were used in the statistical analysis. Aerosols of the graphite powder were generated by a pneumatic dispersion method and those of the fog oil by an evaporation-condensation system. The overall mean aerosol mass concentrations were within 1% of the target levels, and particle sizes were in the respirable range. Mass Median Aerodynamic Diameter of the aerosol mixtures ranged from 0.40 to 0.69 μm. There were no mortalities and no significant exposure-related clinical signs. Lung/body weight ratios were increased in all

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18. SUBJECT TERMS (cont'd)

body weight gain
clinical chemistry
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flow-volume
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graphite
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histopathology
inhalation exposure
light scattering sensor
lung weight/body weight ratio
Mass Median Aerodynamic Diameter
mortality
multivariate analysis
necropsy
obscurant
particle dispersion
petroleum-based liquid
pressure-volume
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aerosol-exposed groups with no recovery observed. Histopathologic findings in all aerosol-exposed groups included hyperplasia of the goblet cells in the respiratory epithelium of the nose, hyperplasia of the epithelium in the lung, hyperplasia of lymphoid tissue in the lung and draining lymph nodes and increased hyaline droplet formation in the proximal convoluted tubule of the kidney. Recovery was seen only for the goblet cell hyperplasia and the increased hyaline droplet formation. Exposure related clinical pathology changes included slight decreases in serum total protein and cholesterol in the two highest aerosol exposure groups, with both parameters showing recovery and a progressive increase in the number of circulating neutrophils. Changes in pulmonary lavage parameters included increased cellularity with significant neutrophil influx and increased lavage fluid protein, with no evidence of recovery. Pulmonary function changes after exposure to the aerosol mixtures were indicative of a mild restrictive lesion characterized by decreased compliance and decreased stati and forced expiratory volumes with partial recovery in all except the 1000 mg/m^3 PBL/200 mg/m^3 graphite group.

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FOREWORD

This Final Report, "Inhalation Toxicity of Single Materials and Mixtures: Phase IV - Thirteen-Week Inhalation Toxicity Study with Aerosol Mixtures of Fog Oil and Graphite Particles in F344/N Male Rats," describes a study conducted by the Life Sciences Research Department of IIT Research Institute (IITRI) for the U.S. Army Medical Research and Development Command under Contract No. DAMD17-89-C-9043 (IITRI Project L06234). The report covers activities for the period of September 1991 through February 1992. This Final Report, originally submitted as a Draft Final Report on July 14, 1992, was accepted without changes by the Research Data Management Division of the U.S. Army Medical Research and Development Command according to a letter dated December 2, 1992. Due to GLP regulations, all signatures within the report are dated after this acceptance date.

Dr. Jack Dacre was the Contracting Officer's Technical Representative. Catherine Aranyi, Principal Investigator, was in charge of the overall conduct and coordination of the program. Dr. Narayanan Rajendran, Aerosol Scientist, Co-Investigator, and Stanley Vana, Inhalation Engineer, were in charge of the test atmosphere generation and monitoring system and the conduct of the aerosol exposures. Dr. John Drummond, Inhalation Toxicologist, was in charge of toxicology operations. As Study Director, Jeannie Bradof was responsible for the overall conduct of the study. Dr. Robert Gibbons, Consultant Biostatistician, provided the statistical design and the overall statistical evaluation of the study. In addition, the following individuals were in charge of various study areas and contributed to this report: Dr. Barry Levine, Consultant, and Mary Ann Cahill - clinical pathology; Dr. M. Tomlinson - histopathology; Dr. Robert Sherwood - pulmonary lavage; Dr. Jeffrey Tepper, Consultant - pulmonary physiology.

Because this is the Final Report for this contract, summary descriptions of the previously submitted reports on Phase I, II and III studies have been included in the "Background" section to bring the reader up to date.

This report is organized in two parts in order to aid the reader in locating and reviewing principal subject areas. Part One, "Experimental Program," summarizes the design, conduct and results of the experimental phases of the program. Appendices to Part One include experimental data tables, the pathology report and the study protocol in toto. The statistical report is presented in Part Two and consists of a list of the significant results followed by a more detailed discussion for each of the various subject areas (body weight gains; food consumption; lung/body weight ratios; clinical chemistry; hematology; hematology differential counts; pulmonary lavage; pulmonary function) included.

Catherine Aranyi

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DISCLAIMER-FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

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__NA__ For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

__NA__ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

Catherine Aranyi 12/22/92

Catherine Aranyi, PI Date

GLP COMPLIANCE STATEMENT

This study was conducted in accordance with U.S. Environmental Protection Agency (EPA) Good Laboratory Practice (GLP) Standards as set forth in the Code of Federal Regulations (Part 792 of Title 40; TSCA), except that all chemical analyses pertaining to the characterization, stability and homogeneity of the bulk test article and attendant documentation were the responsibility of the Sponsor. There were no significant deviations from the aforementioned GLP standards that would have affected the integrity of the study or the interpretation of the test results. The raw data have been reviewed, and the information contained in this report is an accurate representation of the data within the context of the study design and evaluation criteria. All raw data obtained at IITRI will be maintained in the IITRI archives.

Study Director:

Jeannie Bradof

Jeannie Bradof
Research Toxicologist
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12/22/92
Date

EXECUTIVE SUMMARY

This study investigated the potential inhalation hazard of obscurant materials to which military personnel may be exposed during field operations. The objective was to evaluate the potential toxicity of aerosol mixtures by exposing rats in whole-body inhalation chambers under simulated field conditions. This study describes the effects of a 13-week exposure of F344/N male rats conducted 4 hr/day, 4 days/week to mixtures of aerosols of a fog oil (petroleum-based liquid, or PBL) and a solid particulate (graphite) on selected biologic end points. The experimental design included five groups. Four groups were exposed to various graphite/PBL aerosol mixtures and the fifth group was a filtered air control. The four aerosol mixtures tested consisted of the following combinations:

PBL, mg/m^3	Graphite, mg/m^3
250	100
500	100
500	200
1000	200

The rats were exposed in five one-cubic-meter inhalation chambers in a study-dedicated inhalation exposure facility. All animals were monitored for in-life clinical signs and body weights and, in selected groups, for food consumption. In addition, biologic end points including lung/body weight ratios, clinical pathology, histopathology, pulmonary lavage parameters, and pulmonary function were evaluated in animals sacrificed within 24 hr after the last exposure and after a 6-week recovery period.

Aerosols of the graphite powder were generated with a pneumatic dispersion method, and those of the PBL with an evaporation-condensation system. The generators were provided by the Government. The graphite aerosol generator consisted of a screw feeder to meter the test material and a jet mill to aerosolize it. In the fog oil aerosol generator, PBL supplied by a metering pump was evaporated by an immersion heater, and the vapors were condensed to form the PBL aerosol. Aerosol mass concentrations were measured using gravimetric filters collected once per exposure hour. In addition, to maintain control over potential concentration excursions, variations in generator aerosol output were monitored continously by real-time aerosol photosensors. Selected filter-collected aerosol samples were analyzed chemically by gas chromatography (GC) to determine the quantity of PBL and its contribution to the total aerosol mass loading in the PBL/graphite aerosol mixtures.

The overall mean aerosol concentrations for the study ranged from 100 to 101% of the target levels, with % Relative Standard Deviations (%RSDs) ranging from 3.10 to 3.94%. The daily variation

in aerosol concentration (daily %RSD) in all chambers was generally below 10%. PBL aerosol concentrations determined by GC analysis were consistent with gravimetric determinations. The calculated graphite concentrations in the aerosol mixtures, obtained by subtracting the chemically analyzed PBL concentrations from the gravimetrically determined total aerosol concentrations, were also on target. Mass Median Aerodynamic Diameter (MMAD) of each test aerosol mixture was well within the respirable range. The mean MMAD ranged from 0.40 to 0.69 μm. These monitoring data demonstrated that the difficult and complex task of maintaining good control over the exposure concentrations of the individual components in the PBL/graphite aerosol mixtures was successfully accomplished.

A multivariate analysis of variance model was used in the analysis of the clinical chemistry, hematology, hematology differential counts, pulmonary lavage and pulmonary function measurements. Body weight gains and food consumption were analyzed using multivariate analysis of variance for repeated measures. Lung/body weight ratios were analyzed by univariate analysis of variance. In an effort to better approximate the assumed normality of the statistical models, the data were log transformed before analysis. The statistical design, methods and overall statistical evaluation for the study are presented in Part Two of this report entitled: "Statistical Overview of the Results."

There were no mortalities during the study, and clinical observations provided no evidence of any exposure-related toxicity during either the exposure or recovery periods. Exposure to the various aerosol mixtures for 13 weeks had no apparent deleterious effect on body weight gain. The body weight gains of rats exposed to the 500 mg/m^3 PBL/100 mg/m^3 graphite aerosol mixture were significantly greater than those of the control animals during the exposure period, but this finding was considered to be of no toxicologic significance. Similarly, there were no significant differences in food consumption between groups exposed to the aerosol mixtures and the control group during the exposure period. However, during the recovery period the food consumption of all aerosol-exposed groups was significantly greater than that of the controls. The biologic significance of the increased food consumption was not clear.

Lung/body weight ratios were significantly increased in rats from all groups exposed to the PBL/graphite aerosol mixtures at the end of the 13-week exposure period. There was no evidence of recovery as similar increases were also seen in aerosol-exposed rats after the 6-week recovery period. The lung/body weight ratios tended to be increased in a dose-related fashion in both the post-exposure and recovery group rats.

Changes in clinical pathology parameters included slight decreases in serum total protein and cholesterol levels at the end of the 13-week exposure period in animals exposed to aerosol mixtures of 200 mg/m^3 graphite in combination with 500 or 1000 mg/m^3 PBL, but not at the end of the recovery period. Histopathologic changes in

the liver, however, were not in evidence. Exposure-related neutrocytosis was noted for the 1000 mg/m^3 PBL/200 mg/m^3 graphite group at the end of the exposures and for all exposure levels at the end of the recovery period.

Histopathologic evaluation demonstrated that exposure of animals to PBL/graphite aerosol mixtures was associated with reversible hyperplasia of goblet cells in the respiratory epithelium of the nose. Aerosol-exposed animals also developed hyperplasia of epithelium in the lung and hyperplasia of lymphoid tissue in the lung and draining lymph nodes. These changes did not resolve during the recovery period. Hyaline droplet formation in the proximal convoluted tubule of the kidney was exacerbated by exposure to the PBL/graphite aerosol mixtures, but had decreased to post-exposure filtered air control levels by the end of the recovery period. These were all considered exposure-related changes.

Pulmonary lavage of rats exposed for 13 weeks to PBL/graphite aerosol mixtures demonstrated a mild pulmonary inflammatory lesion which failed to resolve after the 6-week recovery period. Pulmonary lavage fluids of rats sacrificed following 13 weeks of exposure to all exposure concentrations of PBL/graphite aerosol mixtures had slight, but significant increases in numbers of cells and protein concentrations as compared to controls. Lavage fluids from rats exposed to 500 mg/m^3 PBL/200 mg/m^3 graphite had an increased percentage of neutrophils.

Animals sacrificed following the 6-week recovery period after 13 weeks of exposure to PBL/graphite aerosol mixtures failed to exhibit recovery of the pulmonary lavage parameters. Total number of cells decreased slightly from the values observed immediately following exposure, but remained significantly higher than control values in rats exposed to PBL and graphite. Lavage fluid protein concentrations remained significantly elevated compared to controls. Percentage of neutrophils in the lung increased over time, indicating that although the lesion was relatively mild immediately after exposure, it was not resolving following the recovery period.

Pulmonary function tests of pressure-volume, flow-volume and gas dilution were performed both immediately post exposure and after a 6-week recovery period. Several parameters were obtained from each of these three tests. Every test showed one or more parameters that were significantly affected by the exposures. Static lung volumes were significantly reduced and a trend toward decreased diffusing capacity was detected; both measurements indicate a stiffer and thickened lung. Compliance, obtained from the pressure-volume curve was reduced, revealing that more pressure was required to expand the lung than normal. Finally, lung volumes were reduced during the latter portion of the flow-volume curve without a reduction in air flow. Overall, the tests indicate that all of the exposure regimens caused a mild restrictive lesion that showed some sign of resolution during the recovery period. However, in the group exposed to the highest combination of the

PBL/graphite aerosol mixtures (1000/200 mg/m^3), regression of the lesion was not observed after the recovery period and the lesion showed signs of small airway restriction that may also have caused peripheral obstruction.

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IITRI PROJECT NO.: L06234

INHALATION TOXICITY OF SINGLE MATERIALS AND MIXTURES: PHASE IV - THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS

PART ONE

EXPERIMENTAL PROGRAM

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JULY 14, 1992

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I. INTRODUCTION AND OBJECTIVES

These studies were sponsored by the U.S. Army Medical Research and Development Command to investigate the potential inhalation hazard of two materials employed as obscurants to which military personnel may be exposed during field operations for short daily durations repeated over irregular periods for a number of weeks. The overall objective was to evaluate the toxicity of aerosols and mixtures of aerosols by exposing laboratory rats in inhalation chambers under simulated field conditions. This program required evaluation of the potential inhalation hazards of aerosols of a solid particulate material (graphite) and mixtures of this solid particulate aerosol with aerosols of fog oil, a petroleum-based liquid (PBL).

The test atmosphere generation and monitoring methods were established in Phase I and the subsequent 4-week study of Phase II evaluated the interaction of concentration, duration and frequency of exposure on selected biologic end points. Based on the statistical evaluation of the results of Phase II, a single daily duration and weekly frequency and the most sensitive biologic end points were selected for the Phase III 4-week exposures. The objective of the 13-week subchronic inhalation toxicity study conducted with male F344/N rats was to determine the effects of longer-term exposure to the aerosol mixtures of fog oil and graphite particles and the reversibility of observed toxic effects after a 6-week recovery period.

The experimental design included five groups. The PBL aerosol was used at three concentrations (250, 500, and 1000 mg/m^3) and the graphite aerosol at two concentrations (100 and 200 g/m^3). The four aerosol mixtures tested consisted of the following combinations: 250 or 500 mg/m^3 PBL with 100 mg/m^3 graphite and 500 or 1000 mg/m^3 PBL with 200 mg/m^3 graphite. The fifth group was a filtered air control. Biologic end points included pulmonary lavage parameters, pulmonary function, lung weights, histopathology, and clinical pathology. These end points were evaluated within 24 hrs after the last exposure and after a 6-week recovery period. All animals on test were monitored for in-life clinical signs, body weights, and selected groups for food consumption. Multivariate and univariate analysis of variance models were used for the statistical evaluation of the data.

II. BACKGROUND: PHASES I, II, and III

1. PHASE I:

The objective of Phase I was the establishment and standardization of the inhalation exposure conditions. The facilities dedicated to the program included two inhalation exposure laboratories with conditioned air supply and chamber air exhaust systems, inhalation exposure chambers with air flow and pressure controls, and aerosol generators provided by the Government. There were seven 1 m^3 inhalation chambers: five were used for exposure to aerosols of the test materials or positive control, and two chambers in a separate room were used to expose the control animals to filtered air. Each of the five exposure chambers was interfaced with two aerosol generators provided by the Government; one for the solid particulate (graphite) aerosols and the second for the petroleum-based liquid (PBL) fog oil. A two-stage filtration system consisting of a bag prefilter and a HEPA filter was used to exhaust the chamber atmospheres.

Aerosols of the graphite particles were generated by pneumatic re-dispersion of the bulk solid using a jet mill and a screw feeder. The solids were delivered by the screw feeder at a constant rate and drawn into the jet mill where they were accelerated to high velocities with the use of compressed air jets. The particles were swept into turbulent motion and pulverized each other. Subsequently, they entered a size classifier and, if small enough, exited the system as aerosol. Large particles remained in the jet mill until their size was reduced enough to pass through the classifier. In order to improve the temporal stability of the solid aerosol generation system at concentrations below 100 mg/m^3, a slip stream dilution system was employed.

Aerosols of the PBL were generated by injecting this fog oil test material onto a Vycor glass heating element in an inert nitrogen atmosphere. The temperature of the heater was monitored by a thermocouple and controlled by a dual set-point temperature controller. The PBL was flash evaporated and condensed quickly to form smoke when mixed with dilution air. The solid particulate aerosol and the PBL smoke were dynamically mixed in a "Y" section before entering the exposure chamber. HPLC analyses of the PBL aerosol collected on the filters revealed that the PBL was not degraded either during the generation process or when mixed with the solid particulate aerosol.

The solids aerosol generator was tested to establish chamber aerosol concentrations within the range of 10 to 200 mg/m^3 (specific levels of 10, 60, 100, and 200 mg/m^3) and the PBL

liquid aerosol generator in the concentration range of 500 to 1000 mg/m^3 (specific levels of 500 and 1000 mg/m^3). Both generation systems functioned without any problem and the aerosol output was stable at these concentration levels.

Three real time optical aerosol sensors were evaluated for monitoring the solid as well as solid-liquid aerosol mixtures. The extreme stickiness of the solid-liquid aerosol mixtures combined with the high electrostatic charge of the solid aerosol produced particle deposition on the sensor's optics and was a major operational problem. Sensors required cleaning after one or two hours of operation. Hence, gravimetric filter collection (at pre-set periodic intervals) was chosen as the primary method for determining the chamber aerosol concentrations. The real time sensors were used to monitor relative concentration variations continuously and serve as a guide for generator adjustment.

For studies with the solid particulate aerosols only, a commercially available, portable continuous aerosol monitor (PCAM) was used to monitor aerosol concentration without any major operational problem. However, over the course of a 4-hr testing period, small drifts were noticeable and daily cleaning of the sensor was necessary. For studies with solid-liquid aerosol mixtures, it was necessary to monitor the concentration at three locations: the solid aerosol generator outlet, the liquid (PBL) aerosol generator outlet, and in the chamber itself. A backscattering photosensor, originally designed at the Oak Ridge National Laboratory (ORNL), was modified in our laboratory to provide a protective air sheath, and was used at the solid generator outlet and in the chamber. The output from the liquid aerosol generator was monitored with the original ORNL photosensor without any modifications.

The particle size distribution of the solid, as well as solid-liquid aerosol mixtures was determined with a Quartz Crystal Microbalance (QCM)-based cascade impactor. The mass median aerodynamic diameter (MMAD) of the solid particulate aerosol was in the range of 1.5 to 2.0 μm and for the solid-liquid aerosol mixture the range was 0.3 to 0.4 μm (for ratio of solid to liquid in the aerosol mixtures, see below). The MMAD of the positive control material (cristobalite), measured with a Mercer Cascade Impactor, was approximately 3.0 μm.

Spatial and temporal homogeneity of the chamber test atmospheres was established through a procedure of simultaneous sampling from several locations within the chambers. Two homogeneity determinations were conducted: the first for the solid particulate aerosols and the second for the solid-liquid aerosol mixtures. The positive control material was tested as part of the solid particulate homogeneity determinations. The test concentrations employed to establish the homogeneity of the chamber atmospheres were:

Graphite aerosols, mg/m^3:	10, 60, 100, 200
Graphite/PBL aerosol mixtures, mg/m^3:	200/500, 200/1000, 0/1000
Cristobalite aerosol, mg/m^3: (positive control)	200

Aerosol mass concentration and particle size were measured at each concentration as a function of location and time. The homogeneity data collected were statistically analyzed to establish the total and individual components of variance, such as effects due to time, shelf, chamber, etc. (A comprehensive report on the statistical analysis prepared by Dr. R. Gibbons, biostatistical consultant to the project, was included in toto in Appendix C of the Phase I report.)

Results of the statistical analysis revealed that the total variation of the aerosol concentration was within the required 20% limits for all the concentration levels tested. For spatial homogeneity, the variation attributable to shelf was always less than 10% for both the solid and solid-liquid aerosol mixtures at all the target levels. For temporal homogeneity, the variation due to time was also less than 10% for all test runs except one (at the 10 mg/m^3 level of the solid aerosol). For the inter-chamber comparison, the aerosol concentration variations between exposure chambers were below 5% at all concentration levels.

For aerosol particle size, the data showed the total variation exceeded 20% most of the time, however, mean particle sizes were always within the inhalable range. In addition, the variation attributable either to shelf or time was always less than 20%, indicating that the variation was not due to non-homogeneity with respect to time or location. Moreover, on an absolute basis the differences in particle size were quite small and therefore were considered to be of no biological significance.

From the results of Phase I, it was concluded that the spatial and temporal homogeneity was adequate for the aerosol concentration and particle size in all the chambers and at all the target concentration levels tested.

2. PHASE II:

The Phase II study was an examination of the effects of inhalation of aerosols of the solid particulate (graphite) test material. According to the objectives of Phase II, a 4-week inhalation toxicity study was conducted to evaluate the effects of exposure concentration of the graphite aerosols, daily duration, and weekly frequency of exposure on selected biologic end points in male and female F344/N rats, to

establish if the sex of the animals affected the results and to evaluate the impact of a recovery period. Biologic end points included pulmonary lavage parameters, pulmonary function, lung weights, histopathology and clinical pathology. These end points were evaluated within 24 hrs after the last exposure and after a 2-week recovery period. In addition, all animals on test were monitored throughout the study for in-life clinical signs, body weights, and, in selected groups, for food consumption. A fractional factorial design, which allowed for the most efficient use of the experimental resources, was used for the statistical evaluation of the study.

The exposures were conducted at two target concentration levels (100 and 200 mg/m^3) of the graphite aerosol for two exposure durations (1 and 4 hrs/day) and two exposure frequencies (2 and 4 days/wk). In addition exposures to cristobalite aerosol (positive control material) were conducted at one concentration (200 mg/m^3) for 4 days/wk and 4 hrs/day. The aerosol test atmospheres of both the graphite and cristobalite powders were generated with the pneumatic aerosol generation systems provided by the Government. The aerosol concentration in the exposure chambers was monitored using gravimetric filters collected once per exposure hour and the concentration variations were monitored in real time with PCAM.

The overall mean aerosol concentrations for the study were generally close to the targets, ranging from 94.4 to 99% for all exposure conditions. The overall Relative Standard Deviation (%RSD) of the concentrations ranged from 2.7 to 9.2%. The daily variation of aerosol concentrations (daily %RSD) in all the chambers was below 10% except on a few occasions, but was never higher than 16.1%. Mass Median Aerodynamic Diameter of the graphite aerosols ranged from 1.2 to 1.6 μm with a Geometric Standard Deviation of 2.4 to 3.1.

The experimental design for the study was prepared in cooperation with Dr. Gibbons, the biostatistical consultant to the program. Because of the complex experimental design mandated by the RFP and the physical limitations (equipment and personnel) of the experimental logistics that required the simultaneous testing of such a large number of conditions under a rigorous schedule, a fractional factorial statistical design was selected which allowed the evaluation of all possible main effects and interactions of the three primary factors and all two-way interactions involving sex and recovery. This design, in conjunction with statistical power computations based on historical data, allowed the use of relatively small group sizes in combination with an "experimental end point day" strategy limited to 4 days after the last exposure and 4 days after the recovery period.

Multivariate analysis of variance models were used to analyze each set of variables (body weight gain, food consumption, relative lung weight, clinical chemistry, hematology, hematology/differential counts, pulmonary lavage, and pulmonary function). Prior to analysis, log transformation of the data was performed on these variables to better approximate the normality assumption of the statistical model. The effects of five factors were examined in these analyses: sex, period (post-exposure or post-recovery), concentration (filtered air control, 100 and 200 mg/m^3 graphite aerosol, or positive control aerosol at 200 mg/m^3), duration (1 or 4 hours per day) and frequency (2 or 4 exposures per week). The animals were allocated to the resulting cells of the design in a fractional factorial manner which allowed the testing of all two-way interactions. Multivariate analysis of variance models were used to analyze the body weight gains and food consumption. Dr. Gibbons's detailed report on the statistical evaluation methods and results were presented in Part Two of the Phase II report.

The results of the statistical computations revealed a remarkably striking absence of significant main effects of any of these factors, suggesting that differences in exposure concentration, frequency, and duration were unrelated to outcome. A notable exception, however, was the pulmonary lavage parameters where several measurements were either significantly increased or decreased.

There were no mortalities, and clinical observations provided no evidence of significant treatment-related toxicity in any experimental group during either the exposure or recovery periods. Overall, the 4-week inhalation exposure to the graphite aerosols had no significant concentration-, duration-, or frequency-related effect on body weight gain. Although statistically significant differences were detected in a number of individual comparisons, the overall results of the study provided little evidence to support the hypothesis that increased exposure to the test article via increased exposure concentration, duration, and/or frequency was associated with significant effects on body weight. Because no consistent, dose-related alterations of body weight gains were observed in groups exposed to the graphite aerosols, it was concluded that the test article had no biologically significant impact on this parameter.

All groups exposed to the graphite or the positive control aerosols demonstrated statistically significant decreases in food consumption when compared to filtered air controls. However, in groups exposed to the graphite aerosol, these decreases were not dose-related, and no consistent effect of concentration, duration, or frequency of exposure were observed.

Neither concentration, duration, nor frequency of exposure of the graphite aerosols affected clinical pathology parameters. Sporadic increases and decreases were seen which were not considered biologically significant. For the positive control group, total WBC counts were slightly, but significantly, elevated at the post-exposure time point for both sexes. These elevations were primarily due to increased numbers of neutrophils. Recovery from this neutrocytosis was not apparent at the post-recovery time point. No other clinical pathology measurements were altered in the positive control group.

Histopathologic evaluation revealed no microscopic lesions related to the test article at the post-exposure or post-recovery time points in animals that had been exposed to the most severe conditions of concentration, duration or frequency. Animals exposed to the positive control developed granulomatous inflammation in the lungs and in the pulmonary and mediastinal lymph nodes. In animals exposed to the test article, pigment was seen within alveolar macrophages or within macrophages in the interstitium and lymphoid tissue of the lung. The presence of pigment in these locations is interpreted as evidence of exposure to the test article but not as a test article-related lesion.

Although the overall effects of inhalation of the graphite particles on relative lung weights were inconsistent, some observations in the high concentration/frequency/duration groups deserve to be noted, as well as the fact that more of these changes appeared post-recovery. These data should be viewed in parallel with the outcome of the lavage parameters.

The pulmonary lavage results indicated that inhalation exposure to graphite aerosols did not alter cellular viability or adversely affect fc-mediated phagocytic activity of alveolar macrophages. This suggested a lack of toxicity to cellular functions from the inhaled graphite aerosols. Pulmonary lavage of graphite-exposed rats indicated the presence of increased numbers of cells, increased amounts of protein and altered types of pulmonary cells and statistical analysis revealed that these data were affected in various ways by exposure duration, frequency and concentration. These changes were consistent with the effects of a pulmonary irritant. All parameters, except for total cells and total viable cells, were within normal limits after the 2-week recovery period.

Tidal breathing, gas dilution, pressure-volume and flow-volume pulmonary function tests were performed both immediately post-exposure and after a 2-week recovery period. Several parameters were obtained from each of these four tests. Every test showed one or more parameters that were significantly affected by the test aerosol or showed strong concentration-related trends. Overall, the tests indicated a mild

restrictive lesion was developing immediately post-exposure, that partially resolved during the recovery period. Tidal breathing tests indicated that tachypnea, a pattern of breathing consistent with restrictive lung disease, occurred. The gas dilution test revealed that lung volumes and diffusing capacity were reduced, indicating a stiffer and thickened interstitium, respectively. Compliance, obtained from the pressure-volume curve and during tidal breathing, was reduced post-exposure, revealing that more pressure was required to expand the lung than normal. Finally, lung volumes were reduced post-exposure during the latter portion of the flow-volume curve without a reduction in air flow. This pattern of response was also suggestive of a mildly restricted lung. The data obtained from the lavage fluid indicating neutrophil influx and accumulation of protein would suggest that a chronic inflammatory response was responsible for the pulmonary function observations. However, since the inflammatory response was greater for the positive control exposure and the pulmonary function response was somewhat less, inflammation cannot be totally explanatory. Overall, the multivariate fractional factorial analysis did not detect any important pulmonary function effects related to the sex of the animals, or the duration and frequency of exposure. Furthermore, the analysis revealed that many of the altered pulmonary measurements recovered to within normal limits during the recovery period. Thus, the Phase II study failed to detect any significant effects of the factors of sex, frequency and duration on pulmonary function parameters.

3. PHASE III:

Based on the overall results of the Phase II study, the "worst case" conditions were selected for Phase III, i.e., a graphite concentration of 200 mg/m^3, a 4-hr daily exposure duration, and an exposure frequency of 4 consecutive days per week. Since some lavage paramaters had not shown recovery at the end of the 2-week period, the recovery period was increased to 3-weeks. Since the sex of the rats generally did not have an impact on the results of the Phase II study, only males were used in Phase III.

The objective of the Phase III study was to determine the effects of 4-weeks of exposure of F344/N male rats (4 hr/day, 4 days/week) to mixtures of aerosols of fog oil and graphite on selected biologic end points. The experimental design included six groups: aerosols of graphite (200 mg/m^3) and of fog oil (1000 and 500 mg/m^3) were each tested alone, and the graphite aerosol was tested in combination with each fog oil concentration. The sixth group was a filtered air control. All animals were monitored for in-life clinical signs and body weights and, in selected groups, for food consumption. In addition, biologic end points including clinical pathology, histopathology, pulmonary lavage parameters, pulmonary

function, pulmonary bactericidal activity, and liver microsomal aryl hydrocarbon hydroxylase (AHH) activity were evaluated in animals sacrificed within 24 hr after the last exposure and after a three-week recovery period.

Aerosol concentrations were measured using gravimetric filters collected once per exposure hour. In addition, to maintain control over potential concentration excursions, variations in generator aerosol output were monitored by real-time aerosol photosensors. Selected filter samples from exposure chambers containing PBL aerosols were analyzed chemically by gas chromatography (GC) to determine the quantity of PBL and its contribution to the total aerosol mass loading in test atmospheres of PBL and graphite aerosol mixtures.

The overall mean aerosol concentrations for the study ranged from 98.5 to 104% of the target levels, with Percent Relative Standard Deviations (%RSDs) ranging from 2.07 to 4.17%. The daily variations in aerosol concentrations (daily %RSDs) in all chambers were generally below 10%. PBL aerosol concentrations determined by GC analysis were consistent with gravimetric determinations. The calculated graphite concentrations in the aerosol mixtures, obtained by subtracting the chemically analyzed PBL concentrations from the gravimetrically determined total aerosol concentrations, were also on target. Mass Median Aerodynamic Diameter (MMAD) of each test aerosol was well within the respirable range and varied from 0.20 μm for PBL (typical size for evaporation/condensation type aerosols) to 1.8 μm for graphite aerosols. The MMAD range for the PBL/graphite mixture was 0.36 to 0.41 μm. These monitoring data demonstrate that, in addition to maintaining the conditions in the chambers with aerosol atmospheres of PBL or graphite only, the difficult and complex task of maintaining good control over the exposure concentrations of the individual components in the PBL/graphite aerosol mixtures was successfully accomplished.

Multivariate analysis of variance models were used in the analysis of the clinical chemistry, hematology, hematology differential counts, pulmonary lavage and pulmonary function measurements. Body weight gains and food consumption were analyzed using multivariate growth curve models. Lung/body weight ratios, pulmonary bactericidal activity and AHH activity were analyzed by univariate analysis of variance. In an effort to better approximate the assumed normality of the statistical models, the above data (with the exception of the AHH activity) were natural log transformed before analysis. The statistical design and methods and the overall statistical evaluation of the studies were presented in Part Two of the Phase III report.

There were no mortalities during the study, and clinical observations provided no evidence of any exposure-related toxicity during either the exposure or recovery periods.

During the exposure period, body weight gains were depressed in rats exposed to graphite, but not in those exposed to PBL. The body weight gains of rats exposed to either of the combined PBL/graphite aerosol mixtures were significantly less than those of rats exposed to graphite alone, and this effect was greater in the mixture with the higher PBL exposure concentration. During the recovery period, body weight gains of graphite-exposed rats remained depressed, but the effect was not enhanced in rats previously exposed to the aerosol mixtures. Thus, there was a recovery from the additional effect of PBL.

Food consumption was decreased during the first two weeks of the exposure period in rats that had inhaled graphite or PBL aerosols. After that time, there were no significant differences in food consumption between groups. The effect of the exposures on food consumption was not enhanced in animals exposed to the PBL/graphite aerosol mixtures. There were no differences in food consumption between treatment groups during the recovery period.

Lung/body weight ratios were significantly increased after both the exposure and recovery periods in graphite-exposed rats, but not in those exposed to PBL. The effect on lung/body weight ratios of the aerosol mixtures was no different from the effect of graphite alone, and there was no evidence of recovery.

The clinical chemistry and hematology parameters were not affected by exposure to aerosols of PBL, graphite or the PBL/graphite mixtures. Sporadic increases and decreases were seen that were not considered biologically significant.

Exposure of animals to aerosols of graphite, PBL or PBL/graphite mixtures was associated with reversible hyperplasia of goblet cells in the respiratory epithelium of the nose. Animals exposed to aerosols of graphite, PBL or their mixtures also developed minimal to mild hyperplasia of the epithelium in the lung which did not resolve after the recovery period. These were both considered test article-related changes.

The activity of the enzyme aryl hydrocarbon hydroxylase (AHH) was used as a marker to identify possible alterations in hepatic cytochrome P_{450} activity occurring as a result of inhalation exposure to graphite and/or PBL aerosols. Small increases in AHH activity were observed in livers from rats in several treatment groups, when compared to filtered air controls. However, these small increases in AHH activity appear to have little biological significance and were not statistically significant. Furthermore, the percentage increases in AHH activity were much smaller than those reported with classically studied enzyme inducers such as polychlorinated biphenyls or 3-methylcholanthrene. No

consistent pattern of alterations in AHH activity was observed at the termination of the recovery period.

Response in pulmonary lavage parameters to graphite aerosol exposure was characterized by increased cellularity with significant neutrophil influx and increased lavage fluid protein. This response was diminished at the end of the three-week recovery period, although increased cell numbers were still evident. PBL aerosol exposure alone initially resulted only in increased numbers of free pulmonary cells. After a three-week recovery period, cell numbers remained high and pulmonary lavage fluid protein levels were slightly elevated. Exposure to PBL/graphite aerosol mixtures initially resulted in less severe pulmonary effects than graphite exposure alone. Pulmonary inflammation decreased during the three-week recovery period as evidenced by amelioration of the neutrophil influx. However, numbers of pulmonary cells remained elevated and lavage fluid protein levels were slightly increased. Pulmonary bactericidal activity was not affected by aerosol exposure to graphite, PBL or PBL/graphite mixtures.

Pulmonary function tests including tidal breathing, static lung volume, pressure-volume and flow-volume tests were performed both immediately post exposure and after a three-week recovery period. Several parameters were obtained from each of these four tests. Every test showed one or more parameters that were significantly affected by the exposure. Overall, the tests indicated that graphite exposure caused a mild restrictive lesion that showed no sign of resolution during the recovery period. Graphite exposure reduced tidal volume and slightly elevated the frequency of breathing, a pattern of breathing consistent with restrictive lung disease. Static lung volumes were significantly reduced and a trend toward decreased diffusing capacity was detected, both measurements indicating a stiffer and thickened lung. Compliance, obtained from the pressure-volume curve, was reduced, revealing that more pressure was required to expand the lung than normal. Finally, lung volumes were reduced in exposed rats during the latter portion of the flow-volume curve without a reduction in air flow. Although all of these measures presented a consistent picture of restrictive lung disease, the absolute changes were small and representative of only a mild functional lesion. Concurrent exposure to PBL neither exacerbated nor ameliorated the response to graphite. The PBL exposure alone caused small increases in resistance suggestive of irritation of the large airways, and an increase in dynamic compliance, a result that is not clearly interpretable. No clear effects of the mixture were observed. The effects of exposure to graphite or PBL had not resolved by the end of the 3-week recovery period in filtered air. However, PBL exposure may have contributed to the persistence of the graphite-induced functional lesion.

III. MATERIALS AND METHODS

1. INHALATION EXPOSURES

1.1 Test Materials

The inhalation exposures were conducted with aerosols generated from a graphite powder and a petroleum-based liquid (PBL) fog oil. Both test articles were provided by the Government. The graphite (Powder A1) and PBL fog oil (SFG-2, MIL-F-12070C & AM 2) test articles were received on September 9, 1991 and May 1, 1989, respectively. All test articles were stored under ambient condition in a secure and environmentally monitored area until used in the aerosol generators.

1.2 Inhalation Exposure Facilities

The inhalation exposure facilities and the methods used for test atmosphere generation and monitoring in this study and described in the following sections have been included in more detail in two of our previous reports. For further reference see the Phase I (test atmosphere development), and Phase II reports, (February 1990 and March 1991, respectively).

This study was conducted in Laboratories I and II (Rooms 1E4-2 and 1E4-3, respectively) of the IITRI/CRB inhalation exposure facility, which was equipped with conditioned air supply and chamber air exhaust systems; inhalation exposure chambers with air flow and pressure controls; and specially designed aerosol generators provided by the Government. There were five Rochester-type, one-cubic-meter inhalation chambers; four of which are located in Laboratory I and were used for exposure to aerosols of the test materials. The chamber used for exposure of the control animals to filtered air was located in a separate room (Laboratory II) to prevent contamination and contact of these animals with the test materials. Laboratory I was maintained at a negative pressure relative to the access corridor and the adjoining Laboratory II which contained the filtered air control chambers.

Supply Air: Both laboratories shared the same supply air but were connected to separate exhaust systems. Single-pass conditioned air was introduced into the rooms at the rate of 18 to 20 changes per hour. Before entering the laboratories, supply air passed through particulate prefilters, charcoal filters, and was preconditioned with a water-cooled air conditioning unit. Temperature and humidity were adjusted to maintain conditions of 21 to 27°C and 30 to 70% relative humidity (RH). An electric duct heater with an automatic control system maintained the required temperature range. Two steam humidifiers, one located at the air conditioning unit outlet and the other in the air inlet duct to the laboratories, supplied the humidity which was controlled with

a high-limit (85%) pneumatic modulating controller. Automatic air handling controls for regulating cooling, heating, and humidity were located in Laboratory I. The conditioned room air was introduced into the chambers through individual inlet filter assemblies consisting of a fiberglass coarse filter and a high efficiency particulate air (HEPA) filter. The air supply was capable of providing a per chamber flow rate of 0.5 equivalent volumes per minute (500 l/min) thus surpassing the minimum flow rate requirement of 0.4 equivalent volumes per minute required for the study.

Exhaust System: The exhaust from each of the aerosol exposure chambers was filtered with a two-stage filtration system and exhausted. The combined exhaust from the four chambers was moved by a pressure blower capable of providing >500 l/min. airflow to each of the exposure chambers against 75 cm of water pressure and was exhausted above the roof outside the building. The individual chamber air flow was controlled with a gate-valve located in the filtered exhaust and monitored with a calibrated orifice meter. The blower was remotely located to minimize noise in the exposure laboratory.

The blower was connected to a redundant power supply. An alarm system installed in the exhaust air system provided warning in case of blower or system failure.

The exhaust system for the filtered air control chamber was independent of the system for the experimental test chambers to avoid potential contamination with the test aerosols. Both exhaust systems were operated continuously except during chamber cleaning or maintenance.

Exhaust Filter System: Air exhausted from each exposure chamber was filtered through a bag-type prefilter followed by a HEPA filter. The prefilter (Cambridge Model 3Z95 fiberglass filter) consisted of five (5) bags or envelopes mounted in a parallel configuration. The filter had a rating of 93-97% efficiency against atmospheric dust, and a holding capacity of 1 gram/cm^2. The backup HEPA filter was also from Cambridge Filter Co. (Model 12X-241212-2, Silver Seal). Both types of filters were mounted separately in epoxy-coated plywood housings. A Magnehelic pressure gauge was used to monitor pressure drop across these filters and determine the filter loading and the need for filter change.

1.3 Aerosol Generation System

The two types of aerosols generators (PBL and graphite) employed in these studies were provided by the Government and developed at the Oak Ridge National Laboratory (ORNL). The two systems were interfaced in a "Y" section just prior to the chamber inlet mixing plenum. Each generation system was operated independently. Individual aerosol generators were used for each inhalation exposure chamber. A brief

description of each of the aerosol generators follows. (For additional details see ORNL final report, J. H. Moneyhun, R. A. Jenkins, R. S. Ramsey and T. M. Gayle "A System for Generating Mixed Aerosols from a Petroleum-Based Liquid and a Fine Solid" March 1989.)

PBL Aerosol Generator: The PBL aerosol generation system employed the evaporation/condensation method for generating the aerosol. The generator system consisted of an immersion heater encased in a stainless steel tube and automatic temperature monitoring and control system (Barber-Coleman Temperature Controller, Model 527Z-40030-014-1-00, Rockford IL). The PBL was delivered to the heater at a constant rate with a metering pump (Eldex, Model E-120-S, San Carlos, CA) where it was flash evaporated. The vapors were transported by nitrogen carrier gas to a glass fixture where it was mixed with dilution air, condensed and delivered to the inhalation chamber. Aerosol concentration was controlled by adjusting PBL delivery rate with the metering pump.

Graphite Aerosol Generator: The graphite powder aerosol generating system consisted of a stainless steel jet mill dispersing unit (Jet-O-Mizer Model 00 Fluid Energy Processing and Equipment Company, Hatfield, PA) fed by a screw-feeder (Series 100 Accurate, Whitewater, WI). The rate of dispersion was controlled by the revolution rate of the feeder-screw. Solids delivered by the screw-feeder into the jet mill funnel were drawn into the mill by aspiration and accelerated to high velocities by two air jets. The particles were swept into turbulent motion and pulverized each other. Consequently, a relatively highly dispersed aerosol was produced at the outlet of the jet mill.

The screw-feeder metering accuracy was improved by the stirrer that vibrated and moved up and down over the feed screw. The stirrer was vibrated by an air driven vibrator. A second vibrator attached to the delivery tube helped prevent packing in the delivery tube.

During the course of the Phase III study one of the jet mills became completely unusable due to erosion of the main body (made of #316 Stainless Steel alloy) and had to be replaced. The erosion was attributed to the impact of high velocity graphite particles on the mill body. Therefore, the operating pressure of the jet mill air was reduced to 35 to 40 psi from the original level of 90 psi. This reduction in pressure prevented erosion without affecting the dispersion process.

In addition, the screw-feeder performance at low feed rates was improved by replacing the original speed controllers with a more precise electronic digital unit.

Typically, the aerosols generated with jet mills are highly charged electrically and it is customary to neutralize the

particles before they enter the exposure chamber. However, the generators used in this study had no provision to neutralize the electric charge. Our discussions with ORNL personnel (developers of the generators) revealed that the graphite test material dispersed under field conditions carries an electric charge and therefore, the laboratory aerosol generators which were designed to simulate the field aerosol had no provisions for aerosol charge neutralization. It is noted that the electric charge on the aerosol modifies the mobility of the particles and alters the deposition onto surfaces.

1.4 Monitoring the Aerosol Test Atmosphere

Aerosol concentration in the exposure chambers was measured by gravimetric filter collection and monitored in real-time with back scattering aerosol sensors. Monitoring the concentration of an electrically charged aerosol in real-time presents a major technical problem; the electrical charge on the aerosol particles modifies their mobility and they tend to deposit on sensing/optical surfaces and produce measurement artifacts leading to a steady drift in the sensor response. Therefore, the real-time sensors could not be used to determine the absolute mass concentration, but were useful in establishing relative changes. In view of these difficulties, the gravimetric method was chosen to be the primary method to monitor the aerosol concentrations. The real-time aerosol sensors were used as on-line guides to keep the aerosol concentrations at target levels. The aerosol particle size was measured with Quartz Crystal Microbalance (QCM).

Exposure Chamber Homogeneity: The spatial uniformity and temporal stability of the aerosol mass concentration and particle size in the exposure chambers were determined during Phase I of the program and was the entire subject of the Phase I report (submitted in February 1990). A brief description of the method is provided below (for a complete description of the methods and discussion of data, see Phase I report). Spatial and temporal homogeneity of the chamber test atmospheres was established through a procedure of simultaneous sampling from ten (10) locations within the chamber. Aerosol mass concentration and particle size were measured at each target level in all the chambers as a function of location and time. Statistical analysis of the data revealed that the variation of the aerosol concentration was within ±20% of the mean in every chamber at all the target concentration levels as required by the RFP (DAMD17-88-R-0049) of this contract.

Aerosol Mass Concentration: Aerosol mass concentration was monitored gravimetrically, approximately once for each hour of the daily exposure period. In addition, real-time sensors were used at the outlet of the PBL and Graphite aerosol generators to monitor generator operation and assist in

keeping the aerosol concentration on target. These photosensors are based on an electro-optical system which measures aerosol concentrations by the principal of back scattering of radiation from a light-emitting diode. As discussed earlier, due to the electrical charge on their surface, the graphite particles could not be kept away from the optics of the sensor and as a result the sensor's calibration could not be maintained. Therefore, the photosensors were employed only as real-time indicators of short term changes in aerosol concentration and as an on-line guide for the laboratory personnel in making necessary adjustments in generator settings when concentration excursions were encountered.

Gravimetric Aerosol Monitoring: The aerosol mass concentration in each chamber was determined by collecting the aerosol on 45 mm diameter glass-fiber filters placed in a closed-face plastic filter holder. The filters have a 99.99% retention efficiency for dioctyl phthalate particles of 0.3 μm. Prior to use, the fiberglass filters were maintained for 24 hours in the conditioned atmosphere of the sampling environment to assure moisture equilibration by the filter pads. The aerosol samples were collected at constant flow rates, using diaphragm-type vacuum air pumps. The filters were weighed on an analytical balance. Dry gas meters connected to the backside of the pumps recorded the corresponding total volume of air sampled. All filter samples were weighed within 15 min of removal from the sampling ports. Samples collected from chambers containing PBL/graphite aerosol mixtures were transferred to screw-cap glass vials. On each exposure day one randomly selected sample from each chamber was submitted for chemical analysis.

Chemical Analysis: Filter-collected samples containing PBL/graphite aerosol mixtures were extracted with methylene chloride and sonicated for 5 min. The samples containing graphite were filtered through a 0.45 μm Teflon filter. The extracts were analyzed (both quantitative and qualitative) by gas chromatography. The basis of the qualitative analysis was a visual comparison of the chromatogram of the bulk PBL to PBL aerosol. Quantitation of PBL was based on measured peak heights of the samples compared to standards prepared from bulk PBL. For additional details on the analytical method and sample preparation procedures, see the Phase I Final Report.

Aerosol Particle Size: The aerosol particle size distribution was monitored by a piezoelectric microbalance-based 10-stage cascade impactor. The Quartz Crystal Microbalance (QCM) is a cascade of aerodynamic-inertial impactors (California Measurements, Sierra Madre, Calif.) in which the suspended particles are classified according to their effective aerodynamic sizes and weighed *in situ* and in real-time on the impaction surface. This is accomplished by using high-frequency, resonating piezoelectric crystals as the impactor

plates. A built-in pump samples the aerosol stream at a rate of 0.24 l/min, separating the aerosol particles into 10 sequential size ranges from 0.07 to 35.4 mm in aerodynamic diameter.

Oxygen Monitoring: A commercial solid-state oxygen analyzer (Lynn Products Co. Inc., Lynn, Mass.) was used to monitor the percentage of oxygen in the chamber atmosphere. Oxygen concentration in each chamber was determined during the first week of the exposures (exposure days 2 and 3).

2. ANIMALS AND MAINTENANCE

2.1 Receipt, Quarantine and Disease Screening Procedures

Two hundred sixty-seven male F344/N rats were obtained from Taconic Farms Inc., Germantown, N.Y., on September 26, 1991. The animals were 4-5 weeks of age at arrival and 6-7 weeks of age at the start of the study. The weight range at arrival was 61 to 106 g.

The animals were observed daily during quarantine. Following randomization, two animals were selected from the excess stock for quarantine sacrifice. These animals were bled and sera sent for a standard rat virus profile (Microbiological Associates, Rockville, Md.) followed by a gross necropsy. No lesions were discovered during the quarantine necropsy, and the test results on all sera were negative.

2.2 Randomization

Rats were assigned to groups prior to exposure initiation using a stratified weight method whereby animals were ranked in order, by weight, and assigned to study groups in random order. The weight range at randomization was 86 to 149 g (weighed and randomized on October 3, 1991). Each rat used in the study was identified by tail tattoo representing a unique number within the population making up the study.

2.3 Housing

The animals were housed in stainless steel wire-mesh inhalation cages suspended over excrement pans lined with deotized cage boards (Shepherd Specialty Papers, Inc., Kalamazoo, MI) on mobile racks which were equipped with an automatic watering system. Each mobile rack held 24 cage units and each cage unit contained four individual cubicles for a total capacity of 96 animals per rack. Each cubicle measured 18.4 x 16.5 x 15.9 cm. The animals were double-housed upon arrival to help them learn to use the automatic watering system. The rats were housed individually at the time of making group assignments and remained individually housed throughout the course of the study. For exposure, the

cages were removed from the racks, and the rats were moved in their cages into the inhalation chambers. The animals were transferred to clean cages weekly, and the cage boards were changed three times per week.

2.4 Food and Water

Purina Certified Rodent Chow No. 5002 and filtered City of Chicago drinking water were available ad libitum during non-exposure hours only.

2.5 Environmental Conditions

During non-exposure periods test animals were held in environmentally controlled holding rooms adjacent to the inhalation exposure laboratories. Separate rooms were used for animals exposed to the test materials and the filtered air controls (1F3-1 and 1F3-2 CRB, respectively). Lighting in the animal rooms was maintained on a 12 hr light/dark cycle. The air supplied to the animal rooms and exposure laboratories was 100% fresh filtered air and provided a minimum of 10 complete air changes per hour. The temperature and relative humidity of the animal rooms were monitored and recorded twice daily on weekdays and once daily on weekends and holidays. Temperature and relative humidity in the individual chambers and the inhalation laboratories were monitored manually at approximately half-hour and hourly intervals, respectively, each exposure day during the animal exposure period with a hand-held electronic thermohygrometer (Cole-Parmer, Chicago, IL). All chamber and laboratory environmental conditions during the animal exposure periods and animal room conditions, with a few minor exceptions, were maintained within specified limits. The following table summarizes these conditions, with results based on the mean of the daily means for Laboratories I and II and the overall mean for the animal rooms. For data on individual chambers, see Section IV.1.5.

	Temp, °C		% RH	
	Mean	Range	Mean	Range
Exposed Animals:				
Animal Room (1F3-1 CRB)	22	21-24	40	33-69
Laboratory I (1E4-2 CRB)	24	22-25	50	36-57
Control Animals:				
Animal Room (1F3-2 CRB)	22	19-24	42	27-69
Laboratory II (1E4-3 CRB)	24	22-25	52	37-61

3. BIOLOGIC END POINTS

3.1 Toxicology, Histopathology and Clinical Pathology

Mortality and Clinical Observations: All animals were observed twice daily on weekdays (once daily on weekends and holidays) for moribundity and mortality. Each animal was formally examined once weekly for clinical signs of pharmacologic and toxicologic effects of the exposure.

Body Weights: The body weights were measured and recorded individually to the nearest whole gram in the morning prior to exposure at study initiation, once weekly during the 13-week exposure and 6-week recovery periods, and immediately before termination. Statistical comparisons were conducted using body weight gains calculated relative to the pre-exposure start weight.

Food Consumption: Food consumption for each animal in the PATH "recovery" groups (for definitions, see Section III.4, Experimental Design and Implementation) was measured weekly during the exposure and recovery phases of the study. A measured amount of food was offered to the rats on the days that body weights were measured. On the next scheduled body weighing day, the remaining food was weighed and replaced with another measured amount of food. The food consumption was calculated as the difference between the amount of food offered and the amount remaining at the end of the session and was expressed as grams of food consumed per day.

Necropsy and Histopathology: Animals remained on the exposure/recovery regimen until the day prior to (within 24 hr of) sacrifice. All necropsies were conducted following specific necropsy procedures. Following *in situ* examination, all organs were dissected from the carcass and protocol-required tissues (nasal turbinates, larynx, trachea, lungs, pulmonary [bronchial] lymph nodes, heart, liver, spleen, kidneys, urinary bladder, stomach, esophagus, adrenals, thymus, brain, sternum and skin) were fixed in 10% neutral buffered formalin. Tails with tattoos used for identification were also saved.

All protocol-required tissues for animals in all treatment groups (post-exposure and post-recovery) were trimmed, processed, embedded in paraffin, sectioned and stained with hematoxylin and eosin (H & E). These tissues were evaluated microscopically and the results tabulated.

Lung Weights: Lung weights (to the nearest 1.0 mg) were obtained from all PATH-designated animals. Lung weight/body weight ratios were calculated using terminal body weights.

Clinical Pathology: Blood samples were collected via the retro-orbital sinus from CO_2-anesthetized PATH rats. Blood collection and same-day analysis of the samples for the hematology and clinical chemistry assays shown below were performed in a predetermined random order.

List of Hematology and Clinical Chemistry Tests

Hematology

Erythrocyte count
Mean corpuscular volume
Mean corpuscular hemoglobin (derived)
Mean corpuscular hemoglobin concentration (derived)
Hemoglobin
Hematocrit (derived)
Erythrocyte morphologic assessment
Leukocyte count
Leukocyte differential count
Platelet count and morphologic assessment

Clinical Chemistry

Total protein
Albumin
Blood urea nitrogen
Creatinine
Alanine aminotransferase
Alkaline phosphatase
Creatine kinase
Total bile acids
Total cholesterol
Glucose
Sorbitol dehydrogenase
Calcium
Inorganic phosphate
Triglycerides

Hematologic determinations were performed with a Baker 9000 hematology analyzer. Quality control assays including normal, abnormal low and abnormal high (Baker Haem-QC Lot Nos. 1305B-1, -2, and -3 and 2006B-1, -2, and -3 for the post-exposure and recovery, respectively, were run twice each day, prior to initiation of test sample assays and again at the end of the day. Clinical chemistry tests were performed with a Beckman Synchron CX5 analyzer. Normal and abnormal quality control samples were run at the beginning of each daily run and before every eighth sample (approximately) throughout the day using Beckman Synchron 1 (Lot No. M102051), Synchron 2 (Lot No. M102052), Synchron 3 (Lot No. M102053), Sigma SDH normal (Lot No. 51H-6129), and Nycomed Diagnostics (Norway) Seronorm (Lot No. 181) and Pathonorm H (Lot No. 26).

The erythrocyte and platelet morphologic assessments were performed during the differential counts of the blood smears which were stained with Wright-Giemsa stain. One hundred leukocytes were identified.

3.2 Pulmonary Lavage

Pulmonary Lavage, Total and Differential Cell Counts: Alveolar macrophages (AM) were obtained by tracheobronchial lavage. The animals were sacrificed by intraperitoneal injection of sodium pentobarbital, and the lungs were lavaged in situ with nine consecutive 6-ml infusions of warm saline. The AM were collected from the lavage fluids by centrifugation (approximately 250 x g for 10 min at 4°C) and resuspended in Hanks Balanced Salt Solution (HBSS) w/o Mg^{++} and Ca^{++} (Whittaker Bioproducts, Walkersville, Md.). The supernatant from the first two washes was saved for protein determination.

Total and viable cell counts were made in a hemacytometer. Cell viability was determined by exclusion of 0.05% trypan blue dye. Determination of the cellular distribution (i.e., percent of AM, polymorphonuclear leukocytes and lymphocytes) was made through differential counts of cytocentrifuge preparations of cells fixed in methanol and stained with Wright's stain.

Pulmonary Lavage Fluid Proteins: Lavage fluid total protein was determined by the method of Bradford (Anal. Biochem. 72:248-254, 1976) using Coomassie Protein Assay Reagent (Pierce, Rockford, Ill.). Triplicate 40 µl aliquots of lavage fluids were placed into replicate wells on a 96-well assay plate, 200 µl of dye reagent added to each well and absorbance read in an ELISA reader at 600 nm (Bio-Tek EL-310, Winooski, Vt.). Readings were compared to a standard curve generated using bovine serum albumin standard (Pierce) by reverse linear regression.

3.3 Pulmonary Function

Preparation: Before pulmonary function testing, the rats were anesthetized with sodium pentobarbital (I.P.) and a cannula was transorally inserted into the trachea using an illuminated small animal laryngoscope. The rats were placed in a whole-body, Plexiglas, flow plethysmograph (BUXCO Electronics, Inc., Sharon, Conn.) for lung function measurements.

Measurement System: Chest wall excursions were detected using a pressure transducer (Validyne Engineering Corp., Northfield, Calif.) connected to the plethysmograph. Airway opening pressure was sensed from a side port in the tracheal cannula using a similar pressure transducer. Analog outputs from these previously calibrated transducer systems were digitized by an on-line microcomputer (BUXCO Electronics, Inc.) and displayed on a scrolling video monitor. When a maneuver was

performed, calculated measurements of pulmonary function were sent to a second microcomputer via a high speed network (LANtastik, Artisoft, Phoenix, Ariz.). The second computer served as the experimenter interface to start maneuvers, monitored the progress of each test and displayed the results.

Pressure-Volume Test: Once the rat was placed in the plethysmograph and before performing the pressure-volume maneuver, the rat lung was slowly inflated (3 ml/sec) to total lung capacity (+30 cm H_2O pressure) and then allowed to relax passively. This procedure ensured that a uniform lung volume history was obtained among animals. During the actual test, the rat was inflated to total lung capacity and then slowly deflated (3 ml/sec) to residual volume (-20 cm H_2O pressure). Vital capacity, the chord slope compliance between 0 and 10 cm H_2O and the peak compliance were obtained from the deflation wing of the resultant pressure-volume curve.

Flow-Volume Test: Small airway integrity was evaluated during forced expiration. Again the rats were given a constant volume history (see above). During the actual maneuver, the rats were slowly inflated to +30 cm H_2O pressure and, under computer control, a solenoid rapidly opened, exposing the rat's airway to -40 cm H_2O pressure. From the resultant maximum expiratory flow-volume curve; forced vital capacity; forced expiratory volume at 50 msec, 100 msec, 200 msec, and 400 msec; peak flow; and flow at 75%, 50%, and 25% of the forced vital capacity were computed.

Gas Dilution Test: Using a syringe attached to a pressure transducer, a volume of test gas equivalent to the vital capacity was injected into the lung and mixed by inflating and deflating the lung ten times. Total lung capacity was obtained by the gas dilution method using 0.5% neon in the test gas (Takezawa et al., J. Appl. Physiol. Environ. Exercise Physiol. 48:1052-1059, 1980). Residual volume was computed as total lung capacity minus vital capacity obtained from the pressure-volume test (see above). Multi-breath diffusing capacity of carbon monoxide was also obtained simultaneously by gas dilution using the 0.5% carbon monoxide in the test gas (Takezawa et al., ibid.).

4. EXPERIMENTAL DESIGN AND IMPLEMENTATION

Report by J. Bradof

4.1 Objectives of the Study

The objective of the thirteen-week inhalation toxicity study conducted with male F344/N rats was to determine the toxic effects of longer-term exposure to the aerosol mixtures of fog oil and graphite particles and the reversibility of observed toxic effects after a 6-week recovery period. Biologic end

points included pulmonary lavage parameters (LAV), pulmonary function (PF), lung weights and histopathology/clinical pathology (PATH). These end points were evaluated in animals sacrificed within 24 hr after the last exposure and after a 6-week recovery period. In addition, all animals on test were monitored throughout the study for in-life clinical signs and body weights, and selected groups (recovery PATH animals) for food consumption.

4.2 Experimental Design

The study design included five exposure groups: the PBL aerosol was tested at three concentrations (250, 500 and 1000 mg/m^3), with the 500 mg/m^3 concentration tested in combination with each of the two concentrations used for the graphite aerosols (100 and 200 mg/m^3), and the low and high PBL concentrations tested in combination with the low and high graphite aerosol concentrations, respectively. The fifth group was a filtered-air control. These combinations were tested in five inhalation chambers as follows:

Group	Chamber No.	Aerosol Concentration, mg/m^3	
		PBL	Graphite
I	6	0	0
II	5	250	100
III	3	500	100
IV	1	500	200
V	2	1000	200

Groups consisting of 40 male F344/N rats were exposed to the above-listed five conditions for 4 hr/day, 4 days/week for 13 weeks. Biologic end points were determined in animals sacrificed within 24 hr after the last exposure (EXP) and after a 6-week recovery period (REC). The distribution of the 200 rats into the end point groups (PATH and LAV/PF) and assay times (EXP and REC) are shown in Table III-1. Rats were shared for the LAV and PF end points. The rats designated for PF/LAV assays on Saturday received an additional exposure on Friday in the last exposure week in order to maintain the same interval between the last exposure and assay for all rats.

TABLE III-1. EXPERIMENTAL DESIGN[a]

Expo. Group[c]	Aerosol Conc., mg/m³ PBL	Aerosol Conc., mg/m³ Graphite	Total Number of Rats	In-Life Testing: Daily Obs[d]	In-Life Testing: Clinical Signs[e]	In-Life Testing: Body Wt.[f]	In-Life Testing: Food Consumpt.[g]	EXP (Post-exposure) Assays[b]: LAV[h]	EXP (Post-exposure) Assays[b]: PF[i]	EXP (Post-exposure) Assays[b]: PATH[j]	REC (Post-recovery) Assays[b]: LAV[h]	REC (Post-recovery) Assays[b]: PF[i]	REC (Post-recovery) Assays[b]: PATH[j]
I	0	0	40	40	40	40	10	10	(8)	10	10	(8)	10
II	250	100	40	40	40	40	10	10	(8)	10	10	(8)	10
III	500	100	40	40	40	40	10	10	(8)	10	10	(8)	10
IV	500	200	40	40	40	40	10	10	(8)	10	10	(8)	10
V	1000	200	40	40	40	40	10	10	(8)	10	10	(8)	10

a Numbers represent sample sizes.
b One (PATH) or two (LAV, PF) assay days occurred at each time point (EXP = within 24 hr of the last exposure; REC = six weeks after the last exposure).
c Exposure Groups II - V were exposed to the aerosol mixtures. Exposure Group I, the control group, was exposed to filtered air.
d Twice/day on weekdays (once/day on weekends) for mortality and moribundity.
e Weekly.
f Weekly for the thirteen-week exposure period and the subsequent six-week recovery period (where applicable) and immediately before termination.
g Weekly for selected animals.
h LAV = Pulmonary lavage assays (see text). These rats were shared with pulmonary function tests, which tested 8 of the available 10 rats.
i PF = Pulmonary function assays (see text). These rats were shared with pulmonary lavage tests.
j PATH = Histopathology/clinical pathology assays (see text).

IV. RESULTS AND DISCUSSION

1. AEROSOL TEST ATMOSPHERE MONITORING
Report by N. Rajendran and S. Vana

1.1 Aerosol Mass Concentration

The graphite and PBL aerosol monitoring results shown in Table IV-1 are presented as overall study means of aerosol mass concentrations determined gravimetrically with associated Standard Deviations (SD) and % Relative Standard Deviations (%RSD). The aerosol mass concentrations represent the total of the graphite and PBL aerosol mixture. These overall means calculated from the daily means were generally close to target levels under all exposure conditions, and ranged from 100 to 101% of the target concentrations. The overall %RSDs for the study ranged from 3.10% to 3.94%.

The daily mean aerosol mass concentrations calculated from the gravimetric filter samples collected in the individual chambers once per hour during the 4-hr exposure durations, along with daily statistical computations are provided in Tables A-1 to A-4 of Appendix A. These data show that the daily mean concentrations were well within the RFP-mandated limits of 20% on all exposure days. In general, the majority of the variations of aerosol concentrations (daily %RSDs) were well below 10% except on six exposure days (see Tables A-1 to A-4 of Appendix A).

1.2 Chemical Analysis

The gravimetric filter samples used to determine the aerosol mass concentrations measure the total aerosol mass loading without any differentiation between contributions of the graphite and PBL components. Therefore, selected filter samples were analyzed by gas chromatography (GC) to quantitate the total amount of PBL collected on the filters. In general, at least one filter was selected at random from each chamber containing PBL aerosol for each exposure day. The GC analysis data revealed that the PBL concentrations were close to the target levels on all occasions and were consistent with the gravimetric determinations.

Table IV-2 presents the PBL aerosol concentration results from GC analyses as overall study means, SDs and %RSDs. The summary data presented in the table demonstrate that the mean PBL aerosol concentrations determined chemically were close to target levels in all chambers and the % mean/target values ranged from 95.2 to 106%. The overall %RSDs ranged from 6 to 12% and were slightly higher than the %RSDs established with the gravimetric method (see Section IV.1.1, above, and Table IV-1), possibly due to the lower number of filters analyzed by the GC procedure than by the gravimetric method.

TABLE IV-1. AEROSOL MASS CONCENTRATION AND PARTICLE SIZE DISTRIBUTION FOR GRAPHITE/PBL AEROSOL MIXTURES

Chamber No./ Exposure Group	Aerosol Mass Concentration, mg/m^3							Particle Size Distribution[b]		
	Target		Gravimetrically Determined[a]							
	PBL	Graphite	Mean	± SD	N[c]	% RSD	% Mean/ Target	MMAD, μm[d]	GSD[d]	N
1/IV	500	200	708	22.23	50	3.14	101	0.69	3.61	8
2/V	1000	200	1213	40.44	50	3.33	101	0.57	3.40	8
3/III	500	100	607	18.84	50	3.10	101	0.44	4.73	8
5/II	250	100	350	13.79	50	3.94	100	0.40	4.42	8

[a]Overall means of the daily aerosol mass concentrations calculated from gravimetrically determined daily averages for the thirteen-week study period
[b]Determined with a quartz crystal microbalance-based cascade impactor
[c]Total number of exposure days in the study
[d]Mass Median Aerodynamic Diameter and Geometric Standard Deviation

TABLE IV-2. SUMMARY OF PBL AEROSOL MASS CONCENTRATIONS DETERMINED BY GAS CHROMATOGRAPHY FROM GRAVIMETRICALLY COLLECTED AEROSOL SAMPLES[a]

Chamber No./ Exposure Group	PBL Aerosol Concentration, mg/m³					% Mean/ Target
	Target	Determined by GC Analysis				
		Mean	± SD	N	% RSD	
1/IV[b]	500[b]	532	62	50	12	106
2/V[b]	1000[b]	1037	78	50	8	104
3/III[c]	500[c]	512	30	49	6	102
5/II[c]	250[c]	238	23	49	10	95.2

[a]Overall means for thirteen-week study period
[b]In addition to PBL aerosol, these test atmospheres contained 200 mg/m³ of graphite aerosol
[c]In addition to PBL aerosol, these test atmospheres contained 100 mg/m³ of graphite aerosol

The daily PBL aerosol concentration determinations for Chambers 1, 2, 3 and 5, along with an overall statistical summary, are provided in Tables A-5 to A-8 of Appendix A. As seen from the tables, PBL aerosol concentration determinations based on GC analysis of individual filters were generally within 20% of the target levels. A further review of the data (Tables A-5 to A-8) clearly shows that the combined as well as individual concentrations of PBL and graphite components of the aerosol mixtures were very close to the intended target concentrations for all chambers which contained the complex aerosol mixtures.

In summary, these monitoring data demonstrate that we have successfully solved the extremely difficult and complex task of maintaining excellent control over the exposure concentrations of the individual components in these PBL/graphite aerosol mixtures.

1.3 Aerosol Particle Size

The aerodynamic particle size distribution of aerosols of the mixtures of PBL and graphite was measured in each chamber eight times during the study using a QCM cascade impactor. The particle size distribution parameters of the aerosols in the exposure chambers are shown in Table IV-1. The Mass Median Aerodynamic Diameter (MMAD) of the mixture of PBL and graphite aerosols ranged from 0.40 to 0.69 μm, with a Geometric Standard Deviation (GSD) of 3.40 to 4.73. The particle size distribution of the aerosol mixture is dominated by the PBL aerosol particle size due to the fact that the mean concentration of the PBL aerosol in the mixture is larger than the graphite (250, 500, or 1000 mg/m^3 of PBL with 100 or 200 mg/m^3 of graphite). All the MMADs of the test aerosols were well within the respirable range (<10 μm diameter).

1.4 Oxygen

The percent oxygen concentration in the individual chambers was determined with a solid state oxygen analyzer twice during the first week of animal exposures. The oxygen concentration was 21.0% in all chambers.

1.5 Chamber Temperature and Humidity

Temperature and relative humidity in the individual chambers were monitored at approximately half hour intervals. The chambers were maintained within the required temperature and humidity ranges of 21-27°C and 30-70%RH, respectively. Summarized information on these conditions with results based on daily means of the measurements are shown in Table IV-3.

TABLE IV-3. THIRTEEN-WEEK SUMMARY OF INHALATION CHAMBER ENVIRONMENTAL CONDITIONS[a]

A: TEMPERATURE

Chamber No.	Graphite/PBL Conc., mg/m^3	T, Avg.[b] °C	±S.D.[c]	Temp., °C min.	Temp., °C max.
1	200/500	24	1	22	25
2	200/1000	24	1	22	25
3	100/500	24	1	22	26
5	100/250	24	1	22	25
6	0/0	24	1	22	25

B: RELATIVE HUMIDITY

Chamber No.	Graphite/PBL Conc., mg/m^3	RH, Avg.[d] %	±S.D.[c]	RH, % min.	RH, % max.
1	200/500	47	4	35	53
2	200/1000	48	4	34	55
3	100/500	48	4	33	54
5	100/250	47	4	33	53
6	0/0	54	4	38	63

[a] Based on daily means calculated from 8 measurements per day for 50 days
[b] Temperature (T) for inhalation chambers was targeted to be 24 ± 3°C
[c] Standard Deviation
[d] Relative humidity (RH) for inhalation chambers was targeted to be 50 ± 20 %RH

2. TOXICOLOGY

Report by J. Drummond

2.1 Survival/Mortality and Clinical Observations

All rats in all exposure groups survived until the scheduled sacrifices. The majority of the rats exhibited no clinical signs of toxicity during either the exposure or recovery periods. Discoloration of the fur by the graphite was evident in all aerosol-exposed animals. However, since the presence of this discoloration was of no toxicologic significance, the discoloration was documented at the start of the study, but not on a continuing basis during the study. Other clinical observations occurred in only a few rats from all exposure groups. The majority of these observations were tail lesions which were in all likelihood mechanical injuries related to the loading of the animal cages in and out of the exposure chambers. The remaining clinical observations occurred sporadically across the exposure groups. The observations were confirmed by the Study Toxicologist. Because of their sporadic occurrence, none of the clinical observations was considered to have any toxicologic significance.

In summary, no animals died during the study and there were no test material-related clinical signs of toxicity in any animal during either the exposure or recovery periods.

2.2 Body Weight

The effects of exposure to the various test atmospheres on body weight gain were evaluated using multivariate analysis of variance for repeated measures. Before analysis the body weight gain data were log-transformed to better approximate the normality assumption of the statistical models. All rats were weighed once weekly, and statistical comparisons were conducted using the body weight gains calculated relative to the pre-exposure start weight. The body weight gain results are summarized in Tables A-9 and A-10 of Appendix A.

Exposure to the various aerosol mixtures for 13 weeks had no apparent deletericus effect on body weight gain. The body weight gains of rats exposed to the 500 mg/m^3 PBL/100 mg/m^3 graphite aerosol mixture were significantly greater than those of the control animals during the exposure period, but this finding was considered to be of no toxicologic significance.

2.3 Food Consumption

The statistical analysis of the food consumption data also employed multivariate analysis of variance for repeated measures. An average daily food consumption was calculated for each weekly measurement period and log-transformed before analysis. The food consumption results are summarized in Tables A-11 and A-12 of Appendix A.

There were no significant differences in food consumption between the groups exposed to the aerosol mixtures and the control group during the exposure period. However, during the recovery period the food consumption of all aerosol-exposed groups was significantly greater than that of the controls. The biologic significance of the increased food consumption is not clear.

2.4 Relative Lung Weights

The relative lung weights (lung/body weight ratios) were analyzed statistically using univariate analysis of variance models on log-transformed data. All data were obtained at necropsy, following either the exposure or recovery periods (see Table A-13 of Appendix A).

Rats from all groups exposed to the aerosol mixtures had significantly increased lung/body weight ratios at the end of the exposure period. There was no evidence of recovery as similar increases were also seen in aerosol-exposed rats after the 6-week recovery period. The lung/body weight ratios tended to be increased in a dose-related fashion in both the post-exposure and post-recovery group rats.

3. CLINICAL PATHOLOGY AND HISTOPATHOLOGY

3.1 Clinical Pathology
Report by B. Levine

Clinical chemistry summary data for post-exposure and post-recovery tests are shown in Table A-14 of Appendix A. Corresponding hematology summary data are in Table A-15 and corresponding hematology WBC differential summary data are in Table A-16.

At the end of the 13-week exposure period, a few clinical chemistry parameters were slightly altered in exposed animals. Slight, but statistically significant decreases in serum total protein and cholesterol levels were seen in animals exposed to aerosol mixtures of 200 mg/m^3 graphite combined with 500 or 1000 mg/m^3 PBL suggesting slight hepatocellular changes. Histopathologic changes in the liver, however, were not in evidence (see Section 3.2). The levels of the liver enzymes ALT and SDH, however, were not elevated for any of the treatment groups. Interestingly, slight decreases in serum ALT were seen in animals exposed to either 500 mg/m^3 PBL/100 mg/m^3 graphite or 1000 mg/m^3 PBL/200 mg/m^3 graphite. The biological significance of these decreases is not known.

No other clinical chemistry changes were considered to be related to exposure. Very slight, but statistically significant decreases in serum calcium levels and increases in

BUN levels occurred in some aerosol-exposed groups. The changes were very small, and concentration-response relationships were not apparent. As such, they were considered unrelated to exposure. Slight, but not statistically significant neutrocytosis was noted for the 1000 mg/m^3 PBL/200 mg/m^3 graphite exposure group. No other hematological parameters were affected by exposure to combinations of PBL and graphite. A very slight, but statistically significant decrease in platelet counts in the 500 mg/m^3 PBL/200 mg/m^3 graphite group was considered spurious and of no biological significance.

At the end of the recovery period, the previously observed slight decreases in serum total protein and cholesterol levels were no longer apparent. All other clinical chemistry changes were considered spurious and unrelated to exposure.

Slight, but statistically significant increases in the number of circulating neutrophils were seen at all exposure levels at the end of the recovery period. On the basis of concentration-response relationships, it is unclear whether PBL or graphite or a combination of these materials was responsible for these increases.

3.2 Histopathology

Report by M. J. Tomlinson

Exposure of animals to PBL/graphite aerosol mixtures was associated with reversible hyperplasia of goblet cells in the respiratory epithelium of the nose. Animals exposed to the aerosol mixtures also developed hyperplasia of epithelium in the lung and hyperplasia of lymphoid tissue in the lung and draining lymph nodes. These changes did not resolve during the recovery period. Hyaline droplet formation in the proximal convoluted tubule of the kidney was exacerbated by exposure to the aerosol mixtures, but had decreased to post-exposure negative control levels by the end of the recovery period. These were all considered test-article related changes. (See complete Pathology Report included in Appendix B.)

4. PULMONARY LAVAGE

Report by R. Sherwood

The results of the pulmonary lavage measurements are shown in Table A-17 of Appendix A. Pulmonary lavage fluids of rats sacrificed following 13 weeks of exposure to all exposure concentrations of PBL/graphite aerosol mixtures had slight, but significant increases in numbers of cells and protein concentrations as compared to controls. Pulmonary cells from rats exposed to 500 mg/m^3 PBL/100 mg/m^3 graphite and 500 or 1000 mg/m^3 PBL combined with 200 mg/m^3 graphite had slightly decreased cellular viability. Lavage fluids from rats exposed

to 500 mg/m^3 PBL/200 mg/m^3 graphite had a decreased percentage of macrophages with an increased percentage of neutrophils.

Animals sacrificed following a 6-week recovery period after 13 weeks of exposure to aerosol mixtures of PBL and graphite failed to exhibit recovery of the pulmonary lavage parameters. Total number of cells decreased slightly from the values observed immediately following exposure, but remained significantly higher than control values in rats exposed to PBL and graphite. Lavage fluid protein concentrations remained significantly elevated compared to controls, although the levels were approximately the same as those observed immediately post-exposure. Pulmonary cells from rats exposed to 500 mg/m^3 PBL/100 mg/m^3 graphite and 500 or 1000 mg/m^3 PBL/200 mg/m^3 graphite continued to have slightly decreased cellular viability. Lavage fluids from all exposure groups had decreased percentage of macrophages with increased percentage of neutrophils.

These data indicate that rats exposed for 13 weeks to PBL/graphite aerosol mixtures had a mild pulmonary inflammatory lesion which failed to resolve after a 6-week recovery period. Total pulmonary cell numbers in the aerosol-exposed rats decreased over the recovery period, but lavage fluid protein levels remained elevated. Percentage of neutrophils in the lung also increased over time, indicating that although the lesion was relatively mild immediately after exposure and after the recovery period, it was not resolving, and may have been deteriorating. This suggests that chronic pulmonary damage may eventually be observed as a result of the subchronic exposure.

5. PULMONARY FUNCTION

Report by J. Tepper

Overall, the pulmonary function data indicate that rats exposed to the complex aerosol mixtures had concentration-related decreases in lung compliance and reduced static and dynamic lung volumes; findings consistent with a mild, restrictive lesion similar to that seen in rats exposed for 4 weeks to graphite aerosols alone (Phase II) or to graphite/PBL aerosol mixtures (Phase III). This statement is supported by multivariate and univariate analyses. Summary data are presented in Table 9 of Part Two, Statistical Overview of the Results. The multivariate analysis, incorporating all 15 parameters from the three subtests (pressure-volume, flow-volume, and gas dilution tests), detected a significant post-exposure treatment effect, but did not find a significant effect in the recovery animals. On the other hand, univariate statistics indicated significant treatment effects in the post-exposure and recovery groups. This difference most likely reflects the limited power of the multivariate tests given the large number of dependent parameters.

In contrast to the results of the 4-week graphite/PBL aerosol mixture study (Phase III), in the 13-week exposure of Phase IV, the PBL in the aerosol mixture appeared to affect the pulmonary function; however, the interaction between PBL concentration and measured dysfunction was complex. Increasing the PBL concentration from 250 to 500 mg/m^3 in the aerosol mixtures, while graphite concentration remained constant (100 mg/m^3), appeared to increase the measured dysfunction. Further increases in PBL (from 500 to 1000 mg/m^3 PBL in combination with graphite at 200 mg/m^3), seemed to be partially protective in the post-exposure group. The concentration-related graphite effect and the complex interaction with PBL did persist into the recovery period. However, the responses in all but the 200 mg/m^3 graphite/ 1000 mg/m^3 PBL group were attenuated and appeared to show some recovery toward the control group response. On the other hand, in the high graphite/high PBL (200/1000 mg/m^3) exposure group, the functional changes were of similar severity in the post-exposure and recovery groups.

5.1 Pressure-Volume Test

Chord compliance and peak compliance were both significantly reduced by all of the complex mixture exposures (Figure IV-1). At the post-exposure period, chord compliance was significantly different for all exposure combinations, while peak compliance was significantly different for all exposure combinations except the lowest concentration mixture (250 mg/m^3 PBL/100 mg/m^3 graphite). The effect of 1000 mg/m^3 PBL/200 mg/m^3 graphite was somewhat less than the 500 mg/m^3 PBL/200 mg/m^3 graphite. For the recovery period, both peak and chord compliance were significantly different from control at all exposure conditions except chord compliance failed to achieve significance for the 500 mg/m^3 PBL/200 mg/m^3 graphite group. Vital capacity, measured from the pressure-volume curve also was significantly reduced for all exposure combinations at the post-exposure period (Figure IV-2). Again, the effect of 1000 mg/m^3 PBL/200 mg/m^3 graphite was somewhat less than the 500 mg/m^3 PBL/200 mg/m^3 graphite. For the recovery period, vital capacity was significantly different from control at all exposure conditions except the 500 mg/m^3 PBL/200 mg/m^3 graphite group.

5.2 Flow-Volume Test

Univariate analyses indicated that forced vital capacity and the forced expiratory volumes at 200 and 400 msec were reduced with all exposure combinations at both the post-exposure (Figure IV-3A) and recovery periods (Figure IV-3B). When the forced expiratory volumes were adjusted for differences in body weight, the forced expiratory volume at 100 msec was also significantly different, but only for all of the post-exposure

FIGURE IV-1 Compliance Measured from the Pressure-Volume Test

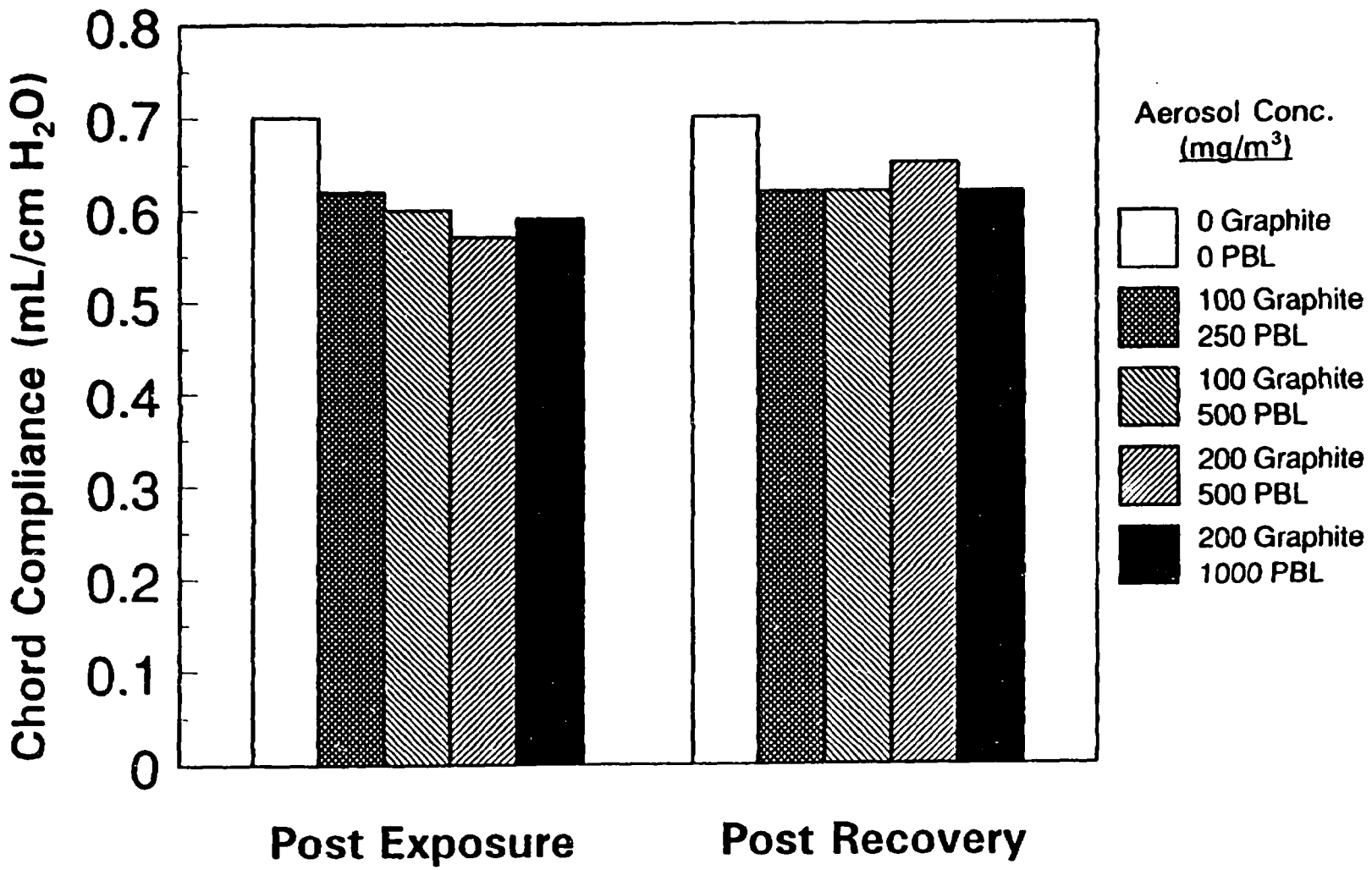
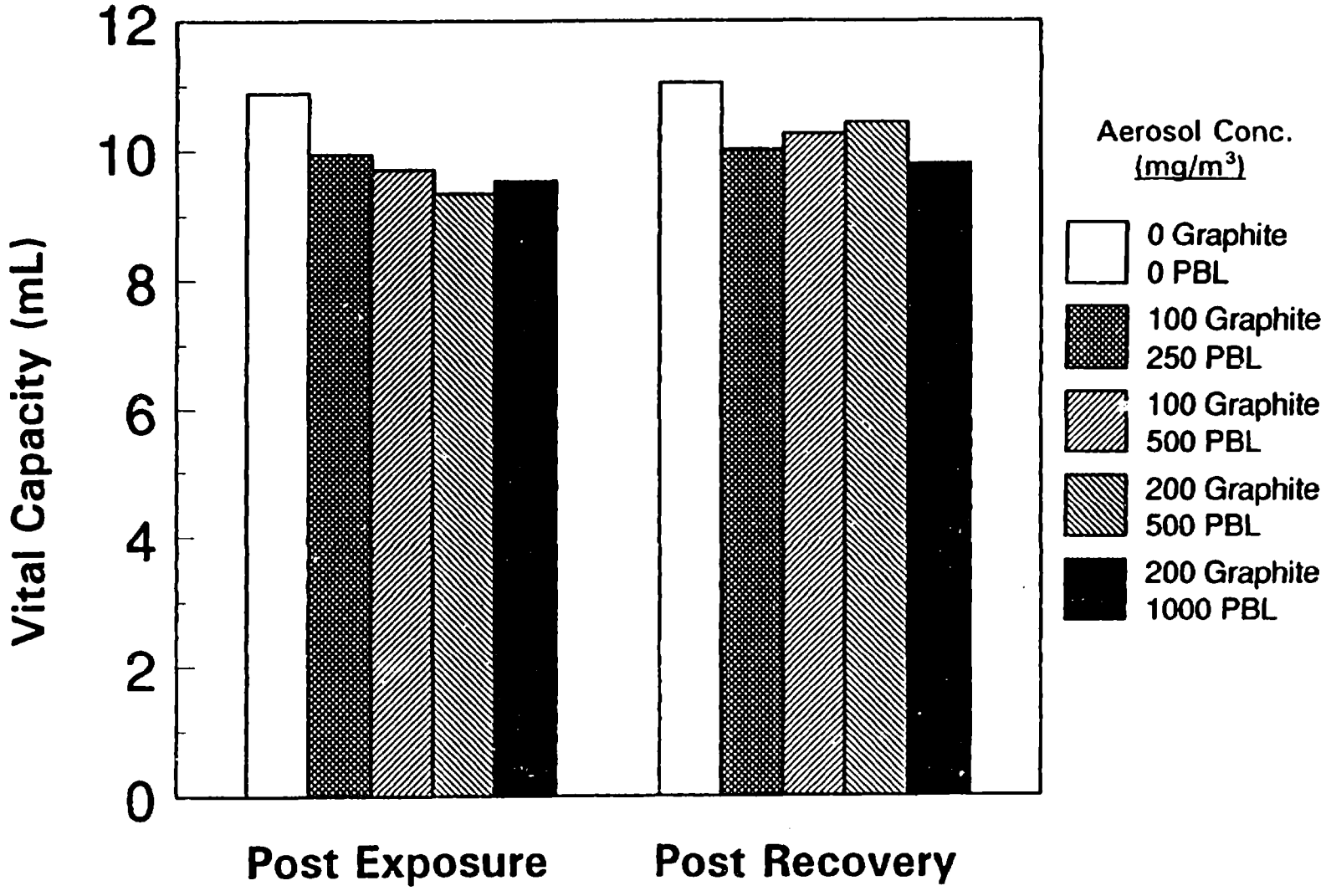


FIGURE IV-2 Vital Capacity Measured During the Pressure-Volume Test



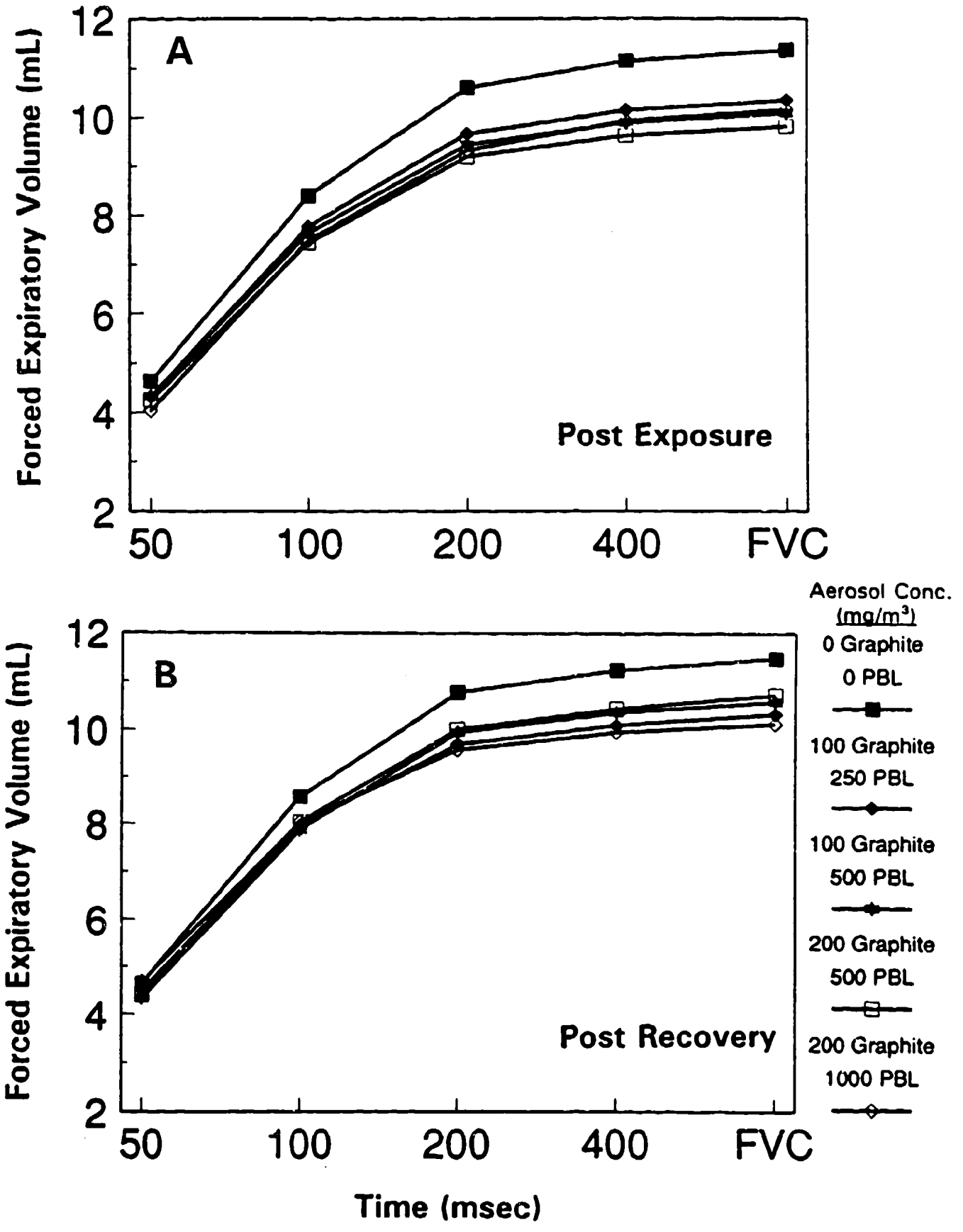


FIGURE IV-3 Forced Expiratory Volume (FVC)

combinations. No significant effects of exposure were detected for any of the flow-derived parameters. When the forced expiratory flows were adjusted for the differences in forced vital capacity, hyperflows were observed in the 1000 mg/m^3 PBL/200 mg/m^3 graphite group (Figure IV-4).

5.3 Gas Dilution Test

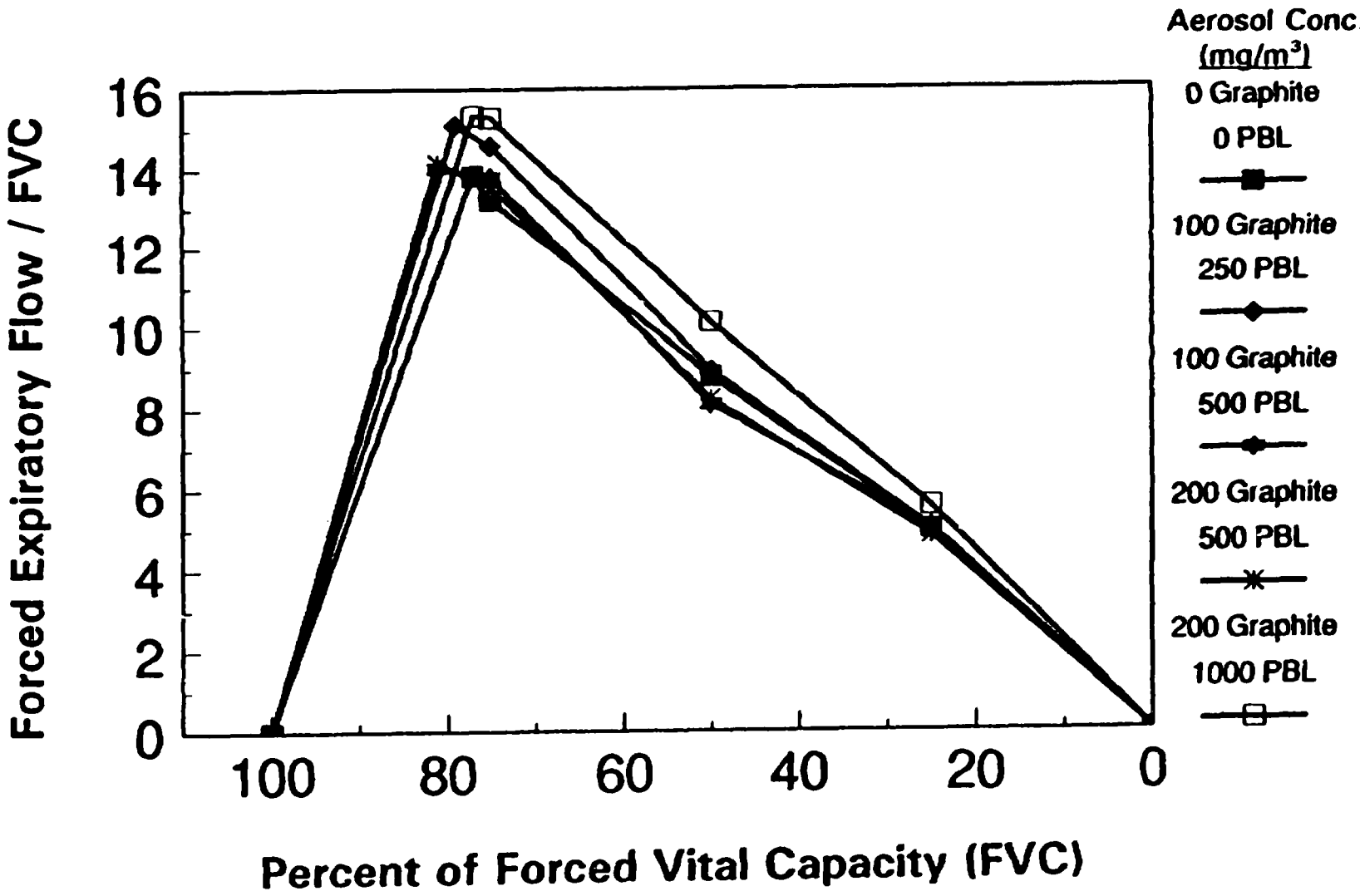
The analysis revealed that a significant decrease in total lung capacity occurred for all exposure combinations at the post-exposure period only. Significant effects were not observed at the recovery period even when the data were adjusted for differences in body weight. The lack of significance in the recovery period is most likely accounted for by the decrease in vital capacity and non statistically significant increase in residual volume (vital capacity + residual volume = total lung capacity). The diffusion capacity of carbon monoxide tended to decrease with increasing graphite and PBL exposure levels, but none of these changes achieved significance either in the post-exposure or recovery period.

5.4 Summary Discussion

Taken collectively, the data suggest that all combinations of PBL and graphite exposure caused the development of a mild restrictive lesion as evidenced by decreased compliance (chord and peak compliance) and by reduced static and forced expiratory lung volumes. Reduced lung compliance specifically indicates that more pressure than normal is required to inflate the lung. The reduction in static lung volumes (total lung capacity, vital capacity and residual volume) as well as the decrease in dynamic measurements of lung volume (forced vital capacity, and forced expiratory volume at 200 and 400 msec) also would indicate an inability of the lung to expand normally. Additionally, the forced expiratory data suggest that the restriction was in the distal lung. The trend in the diffusion data would agree with this conclusion. Although collectively all of these lung function tests present a consistent picture of restrictive lung disease, the absolute changes in the most severely affected measures (vital capacity, forced vital capacity and compliance) were small (11-17% change) and represent only a mild functional lesion.

When the pulmonary function was evaluated post recovery, small, but statistically significant differences remained suggesting that, in general, recovery had not occurred. However, in all of the groups except the 1000 mg/m^3 PBL/200 mg/m^3 graphite group, there tended to be some improvement in lung function. In the 1000 mg/m^3 PBL/200 mg/m^3 graphite group, no sign of recovery was observed. Moreover, additional indices of dysfunction were apparent. Greater than expected flow rates in the volume-corrected forced expiratory

FIGURE IV-4 Post Recovery Flow-Volume Curve



The plotted points represent the flow parameters, PEF, FEF75%, FEF50% or FEF25% divided by FVC plotted vs the %FVC remaining that defines the flow parameters. For the PEF-derived point, %FVC remaining = $\frac{(FVC - VPEF)}{FVC}$ 100

maneuver were observed in this group, suggesting increased severity of the restrictive lesion. Additionally, the nonsignificant 61% increase in residual volume would suggest that the restrictive lesion had progressed such that peripheral obstruction was becoming evident.

V. SUMMARY CONCLUSIONS

This program was funded by the U.S. Army Medical Research and Development Command to investigate the potential inhalation hazard of obscurant materials to which military personnel may be exposed during training and field operations. Such exposures could occur to various concentrations of airborne single materials, or mixtures of materials for short daily durations repeated over different periods for a number of weeks or month. Thus these conditions differ from those encountered by civilian populations in conventional occupational exposures. The objective of these studies was to evaluate the effects of obscurant aerosols and aerosol mixtures by exposing F344/N rats in whole-body inhalation chambers under simulated field conditions.

During the course of the overall program four- and 13-week exposures to aerosols of a petroleum-based liquid fog oil (PBL), or of a solid particulate (graphite) alone, or fog-oil graphite aerosol mixtures were conducted. Aerosols of graphite particles were generated with a jet mill and aerosols of the PBL with an evaporation/condensation method. Aerosol generator output was continuously monitored with photosensors. Aerosol mass concentration was determined hourly by gravimetric filter collection and selected filter samples were analyzed chemically. Aerosol particle size was measured with a Quartz Crystal Microbalance-based cascade impactor. Mean aerosol mass concentrations were close to target levels and particle sizes were in the inhalable range for all studies. Spatial and temporal homogeneity of aerosol concentration and particle size were demonstrated by simultaneous sampling of multiple locations within the exposure chambers. Animals were monitored for clinical signs, body weights and food consumption. Biologic end points including pulmonary function, pulmonary lavage parameters, pulmonary bactericidal activity, clinical pathology and histopathology, were evaluated within 24 hr after the last exposure and after 2- to 6-week recovery periods.

Initially a 4-week exposure of male and female rats to aerosols of graphite particles was conducted to evaluate the effects of exposure concentration (100 and 200 mg/m^3), daily duration (1 and 4 hr), weekly frequency (2 and 4 days/week) and sex of the rats on selected biologic end points. Statistical evaluation of these data based on a fractional factorial design generally demonstrated an absence of significant main effects and interactions suggesting that differences in exposure, duration and frequency and sex of the rats did not significantly affect test results. Based on this information, a 4-week exposure of male rats to aerosols of PBL and graphite, each alone and to their mixtures, was subsequently conducted using a full factorial design with all exposures scheduled for 4 hr/day, on 4 days/week (worst case conditions). The experimental design included six groups:

aerosols of graphite (200 mg/m^3) and of PBL (1000 and 500 mg/m^3) were each tested alone, and the graphite aerosol was tested in combination with each PBL concentration. The sixth group (control) was exposed to filtered air. In this study body weight gains of rats exposed to the PBL/graphite aerosol mixtures were decreased. No rats died and there were no exposure-related signs of toxicity. Treatment-associated changes identified histologically were hyperplasia of goblet cells in the nasal passages and of epithelial cells in the lung. No effects were observed in pulmonary bactericidal activity. Cell numbers and pulmonary lavage protein levels increased after PBL exposure. Graphite aerosols caused an initial increase in cell numbers, lavage fluid protein and neutrophils, which ameliorated after exposure cessation. Overall, four pulmonary function tests (flow-volume, pressure-volume, gas dilution and tidal breathing tests) of anesthetized rats indicated that a mild restrictive functional lesion developed immediately post-exposure to graphite aerosol in both 4-week studies. After the second study the lesion persisted after a 3-week recovery period. PBL aerosol exerted no significant effects on pulmonary function, except for small increases in lung resistance and in dynamic compliance.

The objective of the 13-week study and the principal subject of this report was to determine the effects of longer-term exposures to PBL/graphite aerosol mixtures and the reversibility of any observed toxic effects after a 6-week recovery period. The study was conducted with four groups exposed to PBL/graphite aerosol mixtures consisting of the following combinations: 250 or 500 mg/m^3 PBL with 100 mg/m^3 graphite and 500 or 1000 mg/m^3 PBL with 200 mg/m^3 graphite. The fifth group was a filtered air control. Exposure to the aerosol mixtures resulted in no mortalities, and there were no exposure related clinical signs or significant effects on body weight gain and food consumption. Lung/body weight ratios were increased in a dose-related fashion in all groups exposed to the aerosol mixtures and showed no evidence of recovery.

Slight decreases in serum total protein and cholesterol were seen in rats exposed to 200 mg/m^3 graphite in combination with 500 or 1000 mg/m^3 PBL, however, histopathologic changes in the liver were not in evidence. Minimal increases in the number of circulating neutrophils were seen in rats exposed to the 1000 mg/m^3 PBL/200 mg/m^3 graphite aerosol mixture at the end of the exposure period. By the end of the recovery period the clinical chemistry changes were no longer observed, but neutrocytosis had spread to all aerosol-exposed groups.

Exposure-related histopathologic changes in the 13-week study were essentially the same as those seen in the 4-week studies and included hyperplasia of goblet cells in the respiratory epithelium of the nose, hyperplasia of epithelium in the lung and hyperplasia of lymphoid tissue in the lung and draining

lymph nodes. Again, as in the 4-week studies, only the goblet cell hyperplasia had resolved by the end of the recovery period. After the 13-week exposure, in addition, hyaline droplet formation in the proximal tubule of the kidney was increased in aerosol-exposed rats but returned to control levels during the recovery period.

The results of the pulmonary lavage measurements indicated that rats exposed to PBL/graphite aerosol mixtures for 13 weeks had mild pulmonary inflammation which was characterized by slight increases in cell numbers and protein concentrations. Pulmonary cells from rats exposed to all but the low level (250 mg/m^3 PBL/100 mg/m^3 graphite) had slightly decreased cellular viability. As was the case with the shorter-term studies the changes in the pulmonary lavage parameters failed to exhibit recovery. Cell numbers were somewhat decreased at the end of the recovery period, but lavage fluid protein levels remained high. The percentage of neutrophils in the lung also increased during the recovery period, indicating that although the pulmonary inflammatory changes were relatively mild, the condition of the lung may have actually deteriorated during the recovery period.

A number of the pulmonary function measurements were affected by the 13-week exposures to the aerosol mixtures. In the previous 4-week studies, exposure to graphite aerosols produced a mild restrictive lesion that showed no resolution at the end of the recovery period. When PBL was added to the graphite aerosol, the PBL aerosol neither exacerbated nor ameliorated the response. In the 13-week study a similar mild restrictive functional lesion was observed in all groups exposed to the aerosol mixtures which was characterized by reductions in static lung volumes and diffusing capacity, indicating a stiffer, thickened lung. Compliance was reduced indicating that more pressure was required to expand the lungs and lung volumes were reduced during the latter portion of the flow-volume curve without a reduction in air flow. Although these functional responses were still significantly different from control at the end of the recovery period, there was some evidence of recovery in all exposure groups except the high combination level (1000 mg/m^3 PBL/200 mg/m^3 graphite) where regression of the lesion was not observed.

In summary, the biologic response in F344/N rats after 13 weeks of exposure to the aerosol mixtures was essentially the same as that seen in the previous 4-week study. The histopathologic and pulmonary lavage findings were indicative of a mild inflammatory response and were consistent with other studies in which rats were repeatedly exposed to graphite or PBL singly (Thomson et al., The Toxicologist, 6:134, 1986; Selgrade et al., Tox. Industrial Health, 6:123-143, 1990). The observation of the mild restrictive functional lesion in the lungs of rats exposed to the aerosol mixtures was in contrast to the above-cited studies in which there were not

consistent changes in pulmonary function. However, it should be noted that in the previous study (Thomson et al., cited) the rats were exposed to the graphite aerosols only over a 2-week period.

Thus, the effects observed in the various biologic end points investigated in this study after exposure for 4 hr/day, on 4 days/week for 13 weeks to the PBL/graphite aerosol mixtures were generally mild. By the end of the 6-week recovery period some of the changes showed complete resolution, whereas others demonstrated little or no evidence of recovery.

VI. QUALITY ASSURANCE STATEMENT

Study Title: Thirteen-Week Inhalation Toxicity Study with Aerosol Mixtures of Fog Oil and Graphite Particles in F344/N Male Rats

Project Number: L06234

Study Number: 3

Study Director: J. Bradof

Report Audit Dates: 5/22, 26-28; 6/11-12, 22-26; 7/20-21, 1992

This study has been subjected to inspections and the report, with the exception of the Phase I portion, has been audited by the IITRI Quality Assurance Unit. The report describes the methods and procedures used in the study and the reported results accurately reflect the raw data of the study. There were no significant deviations from the EPA Good Laboratory Practice Standards (Title 40 CFR Part 792).

The following are the inspection dates and the dates inspection reports were submitted:

Dates of Inspection	Inspection Reports Submitted to: Study Director	Management
9/19/91	9/19/91	9/19/91
10/3-4/91	10/04/91	10/04/91
10/08/91	10/08/91	10/08/91
10/11/91	10/11/91	10/11/91
11/08/91	11/08/91	11/08/91
11/12/91	11/12/91	11/12/91
11/21-25/91	11/27/91	12/03/91
12/09/91	12/09/91	12/09/91
1/03/92	1/03/92	1/03/92
1/7-8/92	2/17/92	2/18/92
1/09/92	1/09/92	1/09/92
1/17/92	1/17/92	1/17/92
1/20/92	1/20/92	1/20/92
1/27/92	1/27/92	3/04/92
2/14,20/92	4/24/92	4/24/92
2/25/92	2/25/92	2/25/92
2/27,3/2-4/92	4/07/92	5/05/92
3/03/92	3/03/92	3/03/92
3/04/92	3/04/92	3/05/92
3/09/92	3/09/92	3/09/92
3/11/92	3/11/92	3/11/92

(Continued on next page)

QA Dates - L06234 SN 3 (Continued)

Dates of Inspection	Inspection Reports Submitted to: Study Director	Management
3/24/92	3/24/92	3/24/92
3/30/92	3/30/92	3/30/92
4/7-8/92	4/24/92	4/24/92
4/23-24/92	4/24/92	4/24/92
5/27-28/92	5/28/92	5/28/92
5/29,6/1/92	6/01/92	6/10/92
6/03/92	6/03/92	6/03/92
6/08/92	6/08/92	6/10/92
6/11/92	6/11/92	6/11/92

Ronald A. Boyne, B.S.
Manager, Quality Assurance

12-22-92
Date

VII. PUBLICATIONS AND PRESENTATIONS

Publications and Presentations Resulting from this Contract:

Inhalation Exposure of Laboratory Rats to Aerosol Mixtures of Fog Oil and Graphite for Use as Military Obscurants. Proceedings: Smoke/Obscurants Symposium XVI, 1992, in press. C. Aranyi, N. Rajendran, S.C. Vana, J.N. Bradof, J.G. Drummond, R.L. Sherwood, M.J. Tomlinson, J.S. Tepper, B.S. Levine, R.D. Gibbons, and J.C. Dacre.

Inhalation Exposure of F344/N Male Rats to Aerosol Mixtures for Use as Military Obscurants. Poster presented at the 12th Annual Meeting, American College of Toxicology, October 1991. C. Aranyi, N. Rajendran, S.C. Vana, J.N. Bradof, R.L. Sherwood, J.G. Drummond, M.J. Tomlinson, B.S. Levine, R.D. Gibbons, and J.C. Dacre.

Inhalation Exposure of Laboratory Rats to Aerosol Mixtures of Fog Oil and Graphite for Use as Military Obscurants. Poster submitted for presentation at Smoke/Obscurant Symposium XVI, April 1992. C. Aranyi, N. Rajendran, S.C. Vana, J.N. Bradof, J.G. Drummond, R.L. Sherwood, M.J. Tomlinson, B.S. Levine, R.D. Gibbons, and J.C. Dacre.

Subchronic Inhalation Exposure of Rats to Aerosol Mixtures of Fog Oil and Graphite Used as Military Obscurants. Poster submitted for presentation at the 13th Annual Meeting, American College of Toxicology, October 1992. C. Aranyi, N. Rajendran, S.C. Vana, J.N. Bradof, J.G. Drummond, R.L. Sherwood, M.J. Tomlinson, J.S. Tepper, B.S. Levine, R.D. Gibbons, and J.C. Dacre.

VIII. SIGNATURES OF PERSONNEL WHO CONTRIBUTED TO THE PREPARATION OF THIS REPORT

Catherine Aranyi, Principal Investigator . . . Catherine Aranyi 12/21/92

Narayanan Rajendran, Co-Investigator . . . Narayanan 12/21/92

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Barry Levine, Consultant Clinical Pathologist Barry Levine 12/17/92

Jeffrey Tepper, Consultant Pulmonary Physiologist Jeffrey Tepper 12-18-92

PART ONE

APPENDIX A

TABLES

PART ONE
APPENDIX A

LIST OF TABLES

PART ONE
APPENDIX A

LIST OF TABLES (CONTINUED)

TABLE A-1

DAILY MEAN AEROSOL MASS CONCENTRATIONS OF THE AEROSOL MIXTURE AT THE 700 mg/m^3 TARGET LEVEL (500 mg/m^3 PBL AND 200 mg/m^3 GRAPHITE: CHAMBER 1)

EXPOSURE DAY	CONC. mg/m^3	+/-SD	N*	%RSD	MIN. mg/m^3	MAX. mg/m^3	% MEAN/TARGET
1	669	47	4	7	620	711	96
2	691	53	4	8	617	732	99
3	733	19	4	3	715	754	105
4	753	28	4	4	724	790	108
5	727	23	4	3	702	756	104
6	735	39	4	5	689	784	105
7	725	22	4	3	696	748	104
8	702	18	4	3	675	715	100
9	721	15	4	2	701	735	103
10	708	8	4	1	699	717	101
11	720	19	4	3	698	740	103
12	715	15	4	2	698	733	102
13	710	10	4	1	695	716	101
14	700	19	4	3	682	726	100
15	712	24	4	3	679	735	102
16	718	29	4	4	682	750	103
17	716	26	4	4	689	744	102
18	712	18	4	3	688	731	102
19	729	18	4	2	708	749	104
20	736	27	4	4	700	764	105
21	700	15	4	2	681	714	100
22	697	29	4	4	663	733	100
23	707	14	4	2	686	719	101
24	672	28	4	4	649	712	96
25	645	29	4	4	613	681	92
26	650	60	4	9	608	738	93
27	666	43	4	6	638	730	95
28	677	39	4	6	619	701	97
29	710	43	4	6	649	752	101
30	720	24	4	3	700	753	103
31	740	19	4	3	716	757	106
32	722	27	4	4	706	762	103
33	740	42	4	6	696	798	106
34	722	14	4	2	705	737	103
35	716	16	4	2	695	733	102
36	687	38	4	6	632	722	98
37	693	41	4	6	657	745	99
38	726	36	4	5	699	776	104
39	713	38	4	5	685	767	102
40	721	36	4	5	687	771	103
41	708	27	4	4	693	748	101
42	713	21	4	3	698	743	102
43	688	24	4	3	660	718	98
44	714	39	4	5	681	766	102
45	697	22	4	3	672	726	100
46	695	57	4	8	642	772	99
47	703	22	4	3	683	729	100
48	726	53	4	7	690	804	104
49	708	44	4	6	668	770	101
50	711	31	4	4	686	756	102

* Measurements taken hourly during the daily 4-hour exposure period

STUDY SUMMARY

MEAN	708
STD. DEV.	22.23
% RSD	3.14
N	50
MINIMUM	608
MAXIMUM	804

TABLE A-2

DAILY MEAN AEROSOL MASS CONCENTRATIONS OF THE AEROSOL MIXTURE
AT THE 1200 mg/m^3 TARGET LEVEL
(1000 mg/m^3 PHL AND 200 mg/m^3 GRAPHITE: CHAMBER 2)

EXPOSURE DAY	CONC. mg/m^3	+/-SD	N*	%RSD	MIN. mg/m^3	MAX. mg/m^3	% MEAN/TARGET
1	1261	35	4	3	1219	1298	105
2	1246	98	4	8	1112	1332	104
3	1214	71	4	6	1118	1288	101
4	1242	65	4	5	1176	1317	104
5	1201	17	4	1	1180	1220	100
6	1203	41	4	3	1150	1240	100
7	1088	70	4	6	1022	1180	91
8	1137	48	4	4	1083	1182	95
9	1195	34	4	3	1149	1231	100
10	1242	34	4	3	1196	1274	104
11	1217	66	4	5	1140	1291	101
12	1251	41	4	3	1219	1310	104
13	1214	27	4	2	1195	1254	101
14	1154	28	4	2	1128	1190	96
15	1220	19	4	2	1196	1236	102
16	1170	18	4	2	1157	1196	98
17	1250	28	4	2	1226	1289	104
18	1244	63	4	5	1149	1280	104
19	1261	34	4	3	1225	1301	105
20	1238	24	4	2	1214	1271	103
21	1216	46	4	4	1169	1280	101
22	1226	31	4	3	1180	1249	102
23	1239	68	4	5	1138	1288	103
24	1214	48	4	4	1149	1264	101
25	1196	33	4	3	1147	1214	100
26	1185	38	4	3	1145	1218	99
27	1253	41	4	3	1197	1289	104
28	1216	69	4	6	1154	1279	101
29	1257	42	4	3	1216	1295	105
30	1239	30	4	2	1212	1281	103
31	1242	43	4	3	1201	1300	104
32	1241	51	4	4	1181	1306	103
33	1245	59	4	5	1192	1299	104
34	1262	37	4	3	1228	1303	105
35	1242	47	4	4	1208	1309	104
36	1116	32	4	3	1085	1156	93
37	1197	17	4	1	1176	1211	100
38	1172	13	4	1	1153	1183	98
39	1172	9	4	1	1163	1179	98
40	1129	46	4	4	1074	1187	94
41	1190	42	4	4	1161	1253	99
42	1254	93	4	7	1152	1369	105
43	1246	61	4	5	1159	1289	104
44	1203	124	4	10	1054	1310	100
45	1260	46	4	4	1192	1294	105
46	1202	46	4	4	1164	1268	100
47	1164	42	4	4	1136	1227	97
48	1200	41	4	3	1148	1248	100
49	1205	42	4	3	1171	1266	100
50	1236	29	4	2	1214	1276	103

* Measurements taken hourly during the daily 4-hour exposure period

STUDY SUMMARY

MEAN	1213
STD. DEV.	40.44
% RSD	3.33
N	50
MINIMUM	1022
MAXIMUM	1369

TABLE A-3

DAILY MEAN AEROSOL MASS CONCENTRATIONS OF THE AEROSOL MIXTURE
AT THE 600 mg/m^3 TARGET LEVEL
(500 mg/m^3 PBL AND 100 mg/m^3 GRAPHITE: CHAMBER 3)

EXPOSURE DAY	CONC. mg/m^3	+/-SD	N*	%RSD	MIN. mg/m^3	MAX. mg/m^3	% MEAN/TARGET
1	586	37	4	6	532	616	98
2	607	46	4	8	541	643	101
3	604	18	4	3	585	629	101
4	616	5	4	1	610	623	103
5	599	15	4	2	579	613	100
6	624	11	4	2	608	632	104
7	618	21	4	3	592	638	103
8	616	17	4	3	604	641	103
9	659	17	4	3	645	680	110
10	599	26	4	4	562	622	100
11	612	19	4	3	591	634	102
12	632	16	4	3	610	648	105
13	621	24	4	4	586	640	104
14	601	52	4	9	534	656	100
15	594	23	4	4	568	613	99
16	581	23	4	4	550	601	97
17	609	21	4	3	590	633	102
18	587	15	4	3	567	603	98
19	598	22	4	4	568	615	100
20	591	22	4	4	574	622	99
21	628	47	4	7	599	698	105
22	585	37	4	6	[illegible]5	639	98
23	618	18	4	3	[illegible]0	638	103
24	586	35	4	6	538	617	98
25	609	36	4	6	559	642	102
26	589	39	4	7	536	628	98
27	625	36	4	6	575	659	104
28	620	50	4	8	554	675	103
29	640	39	4	6	586	669	107
30	628	54	4	9	557	680	105
31	590	39	4	7	547	632	98
32	614	40	4	7	557	651	102
33	639	27	4	4	603	667	107
34	623	33	4	5	576	649	104
35	599	45	4	8	544	643	100
36	571	21	4	4	547	592	95
37	586	32	4	5	558	622	98
38	613	10	4	2	601	626	102
39	620	13	4	2	601	631	103
40	634	21	4	3	603	647	106
41	593	22	4	4	563	610	99
42	607	13	4	2	598	626	101
43	603	10	4	2	595	615	101
44	606	31	4	5	574	642	101
45	627	40	4	6	594	684	105
46	594	24	4	4	566	617	99
47	619	26	4	4	587	649	103
48	572	21	4	4	544	595	95
49	581	10	4	2	573	594	97
50	599	10	4	2	586	608	100

* Measurements taken hourly during the daily 4-hour exposure period

STUDY SUMMARY

MEAN	607
STD. DEV.	18.84
% RSD	3.10
N	50
MINIMUM	532
MAXIMUM	698

TABLE A-4

DAILY MEAN AEROSOL MASS CONCENTRATIONS OF THE AEROSOL MIXTURE
AT THE 350 mg/m^3 TARGET LEVEL
(250 mg/m^3 PBL AND 100 mg/m^3 GRAPHITE: CHAMBER 5)

EXPOSURE DAY	CONC. mg/m^3	+/-SD	N*	%RSD	MIN. mg/m^3	MAX. mg/m^3	% MEAN/TARGET
1	335	21	4	6	307	357	96
2	339	59	4	18	270	415	97
3	320	100	5	31	150	413	91
4	331	9	4	3	325	344	95
5	352	37	4	10	328	406	101
6	362	27	4	7	346	402	103
7	382	65	5	17	314	480	109
8	338	16	4	5	314	349	97
9	369	18	4	5	346	386	105
10	361	17	4	5	342	379	103
11	371	14	4	4	350	378	106
12	361	20	4	6	338	386	103
13	348	5	4	1	340	351	99
14	351	7	4	2	343	359	100
15	352	20	4	6	334	380	101
16	346	8	4	2	338	357	99
17	329	15	4	5	308	344	94
18	357	10	4	3	351	371	102
19	368	22	4	6	335	385	105
20	372	22	4	6	353	395	106
21	355	17	4	5	337	374	101
22	335	3	4	1	332	338	96
23	365	27	4	7	327	392	104
24	346	9	4	3	338	359	99
25	344	25	4	7	319	368	98
26	350	37	4	11	310	399	100
27	336	18	4	5	320	359	96
28	341	22	4	6	319	364	97
29	371	21	4	6	349	392	106
30	351	6	4	2	343	356	100
31	351	11	4	3	336	363	100
32	359	17	4	5	338	380	103
33	351	29	4	8	309	373	100
34	356	15	4	4	336	369	102
35	348	24	4	7	328	382	99
36	336	27	4	8	301	367	96
37	342	16	4	5	332	366	98
38	374	14	4	4	365	395	107
39	364	23	4	6	345	397	104
40	335	11	4	3	320	346	96
41	345	24	4	7	311	367	99
42	344	21	4	6	323	373	98
43	343	11	4	3	333	358	98
44	338	29	4	9	311	370	97
45	340	11	4	3	332	356	97
46	322	16	4	5	303	339	92
47	342	12	4	4	331	355	98
48	349	19	4	5	323	368	100
49	364	24	4	7	342	393	104
50	351	14	4	4	338	367	100

* Measurements taken hourly during the 4-hour exposure period

STUDY SUMMARY

MEAN	350
STD. DEV.	13.79
% RSD	3.94
N	50
MINIMUM	150
MAXIMUM	480

TABLE A-5

GC ANALYSIS OF PBL FROM GRAVIMETRIC FILTER SAMPLES
AT THE 700 mg/m^3 TARGET LEVEL
(500 mg/m^3 PBL AND 200 mg/m^3 GRAPHITE: CHAMBER 1)

SAMPLE NUMBER	EXPOSURE DAY	AMOUNT COLLECTED (mg)	VOLUME SAMPLED (L)	SAMPLE CONC. (mg/m^3)	PBL ANALYZED (mg)	PBL CONC. (mg/m^3)	CHEM. /GRAV. RATIO
004	1	54.4	76.5	711	39.6	518	0.73
018	2	51.4	70.2	732	31.8	453	0.62
033	3	53.3	74.5	715	42.4	569	0.80
051	4	51.8	69.7	743	18.0	258	0.35
069	5	50.4	68.8	733	37.2	541	0.74
083	6	58.0	79.9	726	42.0	526	0.72
099	7	53.6	72.8	736	32.8	451	0.61
117	8	52.3	73.1	715	38.2	523	0.73
133	9	55.6	75.6	735	40.2	532	0.72
147	10	51.2	71.4	717	33.6	471	0.66
165	11	55.0	75.3	730	42.4	563	0.77
179	12	53.3	73.9	721	33.8	457	0.63
197	13	54.4	76.2	714	42.0	551	0.77
213	14	54.1	74.5	726	44.2	593	0.82
230	15	52.2	72.2	723	38.6	535	0.74
246	16	60.7	83.0	731	51.4	619	0.85
260	17	62.0	84.7	732	54.4	642	0.88
277	18	57.6	80.4	716	43.2	537	0.75
293	19	60.9	84.4	722	49.6	588	0.81
310	20	63.7	86.4	737	51.2	593	0.80
323	21	59.3	83.0	714	42.4	511	0.72
339	22	60.6	82.7	733	42.4	513	0.70
357	23	60.3	84.7	712	50.2	593	0.83
371	24	59.3	83.3	712	40.4	485	0.68
387	25	55.4	81.3	681	41.6	512	0.75
406	26	57.3	77.6	738	40.4	521	0.71
419	27	58.3	79.9	730	40.8	511	0.70
438	28	54.0	77.0	701	40.6	527	0.75
453	29	54.8	76.5	716	36.4	476	0.66
470	30	58.2	80.7	721	38.0	471	0.65
484	31	59.0	82.4	716	47.6	578	0.81
500	32	59.4	83.8	709	48.0	573	0.81
518	33	60.0	82.1	731	50.2	611	0.84
532	34	58.6	81.8	716	42.8	523	0.73
547	35	54.8	77.0	712	36.8	478	0.67
563	36	57.8	80.1	722	44.2	552	0.76
580	37	57.8	82.1	704	45.0	548	0.78
598	38	61.7	84.7	728	51.6	609	0.84
614	39	59.6	83.8	711	51.6	616	0.87
630	40	60.6	84.7	715	51.0	602	0.84
643	41	61.6	82.4	748	42.6	517	0.69
661	42	60.8	86.9	700	48.8	562	0.80
677	43	62.6	87.2	718	45.2	518	0.72
692	44	63.5	88.1	721	47.8	543	0.75
707	45	62.1	85.5	726	42.8	501	0.69
726	46	54.8	78.4	699	42.4	541	0.77
742	47	58.0	81.3	713	42.8	526	0.74
757	48	54.5	76.7	711	35.8	467	0.66
773	49	56.4	80.4	701	40.6	505	0.72
789	50	57.5	81.3	707	46.4	571	0.81

STUDY SUMMARY

MEAN	532	0.74
STD. DEV.	62	0.09
% RSD	12	12.16
N	50	50
MINIMUM	258	0.35
MAXIMUM	342	0.88

TABLE A-6

GC ANALYSIS OF PBL FROM GRAVIMETRIC FILTER SAMPLES
AT THE 1200 mg/m^3 TARGET LEVEL
(1000 mg/m^3 PBL AND 200 mg/m^3 GRAPHITE: CHAMBER 2)

SAMPLE NUMBER	EXPOSURE DAY	AMOUNT COLLECTED (mg)	VOLUME SAMPLED (L)	SAMPLE CONC. (mg/m^3)	PBL ANALYZED (mg)	PBL CONC. (mg/m^3)	CHEM. /GRAV. RATIO
008	1	64.6	53.0	1219	62.4	1177	0.97
024	2	65.8	53.2	1237	49.6	932	0.75
039	3	66.3	53.5	1239	57.6	1077	0.87
054	4	67.6	53.0	1275	59.4	1121	0.88
070	5	64.9	53.2	1220	56.8	1068	0.88
087	6	66.7	53.8	1240	60.6	1126	0.91
103	7	79.6	67.4	1181	62.4	926	0.78
121	8	83.0	70.2	1182	69.2	986	0.83
136	9	86.4	70.2	1231	69.8	994	0.81
152	10	90.1	72.8	1238	77.4	1063	0.86
168	11	90.7	72.8	1246	75.2	1033	0.83
183	12	88.0	72.2	1219	67.0	928	0.76
199	13	86.6	71.6	1209	67.8	947	0.78
216	14	87.2	73.3	1190	72.6	990	0.83
231	15	88.2	72.8	1212	68.4	940	0.78
248	16	87.4	73.1	1196	78.8	1078	0.90
263	17	87.8	71.6	1226	76.6	1070	0.87
281	18	91.1	71.9	1267	86.4	1202	0.95
295	19	88.8	72.5	1225	74.8	1032	0.84
311	20	88.4	72.8	1214	77.6	1066	0.88
330	21	74.9	62.0	1208	73.8	1190	0.99
346	22	76.0	61.7	1232	68.6	1112	0.90
362	23	80.6	63.7	1265	64.0	1005	0.79
377	24	79.4	65.1	1220	74.0	1137	0.93
392	25	79.0	65.1	1214	63.6	977	0.81
408	26	79.2	65.1	1217	70.6	1084	0.89
426	27	80.0	64.0	1250	74.2	1159	0.93
441	28	81.0	63.7	1272	69.4	1089	0.86
456	29	78.2	64.3	1216	59.8	930	0.76
474	30	79.6	65.7	1212	63.4	965	0.80
489	31	81.1	66.6	1218	56.6	850	0.70
503	32	82.8	66.8	1240	68.4	1024	0.83
521	33	79.9	66.8	1196	68.0	1018	0.85
538	34	82.0	66.8	1228	73.6	1102	0.90
553	35	79.7	66.0	1208	68.2	1033	0.86
568	36	79.9	69.1	1156	76.2	1103	0.95
585	37	81.6	67.4	1211	73.6	1092	0.90
602	38	75.0	63.4	1183	61.2	965	0.82
616	39	76.5	64.9	1179	69.2	1066	0.90
634	40	80.0	67.4	1187	78.0	1157	0.98
647	41	84.1	67.1	1253	72.4	1079	0.86
666	42	82.2	67.7	1214	67.6	999	0.82
682	43	84.4	67.7	1247	68.4	1010	0.81
696	44	88.3	67.4	1310	66.2	982	0.75
712	45	85.9	67.7	1269	63.8	942	0.74
728	46	83.3	65.7	1268	66.6	1014	0.80
746	47	80.6	65.7	1227	63.4	965	0.79
760	48	81.6	65.4	1248	68.6	1049	0.84
776	49	78.9	65.7	1201	66.8	1017	0.85
793	50	79.0	65.1	1214	64.2	986	0.81

STUDY SUMMARY

MEAN	1037	0.85
STD. DEV.	78	0.07
% RSD	8	7.77
N	50	50
MINIMUM	850	0.70
MAXIMUM	1202	0.99

TABLE A-7

GC ANALYSIS OF PBL FROM GRAVIMETRIC FILTER SAMPLES
AT THE 600 mg/m^3 TARGET LEVEL
(500 mg/m^3 PBL AND 100 mg/m^3 GRAPHITE: CHAMBER 3)

SAMPLE NUMBER	EXPOSURE DAY	AMOUNT COLLECTED (mg)	VOLUME SAMPLED (L)	SAMPLE CONC. (mg/m^3)	PBL ANALYZED (mg)	PBL CONC. (mg/m^3)	CHEM. /GRAV. RATIO
010	1	70.1	113.8	616	54.0	475	0.77
026	2	73.2	115.5	634	63.2	547	0.86
042	3	71.5	113.6	629	63.8	562	0.89
059	4	68.8	111.6	616	62.6	561	0.91
074	5	69.1	112.7	613	57.2	508	0.83
090	6	69.9	111.9	625	55.0	492	0.79
109	7	82.2	130.3	631	61.2	470	0.74
123	8	78.8	128.6	613	65.2	507	0.83
139	9	82.1	127.2	645	67.0	527	0.82
158	10	80.8	130.0	622	68.8	529	0.85
174	11	79.5	128.3	620	*		
189	12	79.9	126.9	630	67.6	533	0.85
203	13	79.9	128.3	623	60.6	472	0.76
220	14	71.6	114.7	624	53.4	466	0.75
236	15	76.4	124.6	613	65.8	528	0.86
254	16	74.7	124.3	601	65.8	529	0.88
270	17	75.7	122.1	620	62.8	514	0.83
284	18	70.2	116.4	603	56.0	481	0.80
300	19	77.5	126.3	614	65.2	516	0.84
318	20	74.3	119.5	622	60.4	505	0.81
331	21	74.3	122.3	608	60.0	491	0.81
348	22	75.3	117.8	639	66.6	565	0.88
364	23	71.4	113.6	629	56.0	493	0.78
382	24	70.4	114.1	617	59.2	519	0.84
395	25	67.4	107.6	626	57.8	537	0.86
414	26	67.8	107.9	628	52.4	486	0.77
427	27	69.8	112.1	623	52.4	467	0.75
443	28	71.0	112.7	630	57.6	511	0.81
459	29	69.0	108.5	636	57.0	525	0.83
475	30	74.2	119.8	619	56.8	474	0.77
492	31	77.4	126.3	613	61.0	483	0.79
507	32	77.9	126.6	615	56.2	444	0.72
525	33	74.3	123.2	603	63.0	511	0.85
540	34	80.9	129.7	624	70.0	540	0.87
555	35	72.2	115.3	626	58.0	503	0.80
573	36	77.3	130.6	592	66.2	507	0.86
590	37	81.0	130.3	622	74.0	568	0.91
604	38	79.7	129.7	614	71.2	549	0.89
620	39	78.4	126.3	621	68.4	542	0.87
637	40	79.1	131.1	603	74.2	566	0.94
652	41	80.8	132.5	610	71.2	537	0.88
667	42	78.9	131.1	602	68.0	519	0.86
686	43	82.6	134.2	615	71.6	534	0.87
700	44	82.7	133.7	619	64.2	480	0.78
718	45	83.2	133.7	622	68.6	513	0.82
731	46	77.7	126.0	617	66.8	530	0.86
747	47	77.8	126.6	615	63.8	504	0.82
766	48	74.1	124.6	595	63.8	512	0.86
780	49	76.7	129.1	594	63.2	490	0.82
796	50	76.6	126.9	604	61.2	482	0.80

* Sample lost in preparation

STUDY SUMMARY

MEAN	512	0.83
STD. DEV.	30	0.05
% RSD	6	5.86
N	49	49
MINIMUM	444	0.72
MAXIMUM	568	0.94

TABLE A-8

GC ANALYSIS OF PBL FROM GRAVIMETRIC FILTER SAMPLES
AT THE 350 mg/m^3 TARGET LEVEL
(250 mg/m^3 PBL AND 100 mg/m^3 GRAPHITE: CHAMBER 5)

SAMPLE NUMBER	EXPOSURE DAY	AMOUNT COLLECTED (mg)	VOLUME SAMPLED (L)	SAMPLE CONC. (mg/m^3)	PBL ANALYZED (mg)	PBL CONC. (mg/m^3)	CHEM. /GRAV. RATIO
015	1	57.8	161.7	357	39.0	241	0.68
032	2	50.0	147.0	340	30.8	210	0.62
048	3	53.6	148.1	362	35.2	238	0.66
064	4	54.6	158.9	344	37.0	233	0.68
078	5	61.0	150.1	406	37.6	250	0.62
094	6	54.9	155.8	352	34.8	223	0.63
111	7	81.7	214.9	380	47.0	219	0.58
127	8	61.8	177.3	349	47.4	267	0.77
146	9	64.2	177.0	363	46.0	260	0.72
161	10	68.5	184.4	371	39.8	216	0.58
176	11	64.7	171.1	378	37.0	216	0.57
192	12	63.8	174.5	366	33.8	194	0.53
209	13	59.4	169.1	351	34.0	201	0.57
226	14	57.2	159.4	359	40.2	252	0.70
240	15	63.8	167.7	380	43.2	258	0.68
255	16	61.3	171.6	357	39.4	230	0.64
273	17	61.0	177.3	344	48.4	273	0.79
289	18	64.7	174.2	371	50.2	288	0.78
306	19	62.5	166.8	375	47.2	283	0.76
319	20	61.6	174.5	353	40.4	232	0.66
337	21	62.8	172.8	363	44.0	255	0.70
353	22	57.0	168.8	338	35.6	211	0.62
369	23	59.3	161.4	367	45.6	283	0.77
385	24	56.3	156.9	359	38.0	242	0.67
400	25	56.8	156.9	362	39.4	251	0.69
416	26	58.0	165.1	351	33.0	200	0.57
432	27	55.2	153.8	359	31.0	202	0.56
449	28	55.8	153.5	364	*		
463	29	57.9	162.0	357	33.4	206	0.58
480	30	55.3	155.2	356	36.8	237	0.67
495	31	58.1	163.4	356	33.4	204	0.57
511	32	59.5	164.0	363	35.2	215	0.59
527	33	59.6	162.6	367	37.4	230	0.63
544	34	57.0	155.8	366	37.2	239	0.65
561	35	60.3	157.7	382	36.6	232	0.61
577	36	53.5	145.8	367	36.6	251	0.68
592	37	56.0	153.2	366	36.4	238	0.65
609	38	59.0	161.7	365	42.8	265	0.73
623	39	57.5	160.3	359	35.2	220	0.61
641	40	56.8	164.3	346	43.6	265	0.77
657	41	57.2	161.1	355	36.8	228	0.64
673	42	59.2	158.9	373	40.4	254	0.68
689	43	59.4	165.7	358	39.6	239	0.67
704	44	58.0	164.0	354	38.8	237	0.67
722	45	56.2	158.0	356	41.6	263	0.74
737	46	55.9	165.1	339	40.8	247	0.73
752	47	59.1	166.5	355	38.6	232	0.65
768	48	58.3	158.6	368	39.6	250	0.68
784	49	61.6	164.0	376	41.2	251	0.67
800	50	57.0	158.3	360	38.6	244	0.68

* Sample lost in preparation

STUDY SUMMARY

MEAN	238	0.66
STD. DEV.	23	0.06
% RSD	10	9.80
N	49	49
MINIMUM	194	0.53
MAXIMUM	288	0.79

TABLE A-9
SUMMARY OF BODY WEIGHT GAINS (g) OF MALE RATS
(EXPOSURE PERIOD)

GROUP	GRAPHITE mg/m³	PBL mg/m³		Study Day 5	12	19	26	33	40	47	54	61	68	75	82	89
I	0	0														
			mean	12.85	39.05	57.10	77.45	95.83	110.50	124.28	137.78	151.85	162.15	174.78	183.28	194.53
			sd	2.84	5.81	8.39	10.51	12.71	14.72	16.63	16.96	18.64	19.89	20.41	20.79	21.89
			n	40	40	40	40	40	40	40	40	40	40	40	40	40
II	100	250														
			mean	11.75	38.08	56.72	78.43	95.68	113.08	128.02	143.65	155.55	167.65	178.73	186.72	197.73
			sd	3.76	4.77	7.74	9.36	11.18	12.65	13.74	14.75	15.82	16.25	17.08	19.59	18.34
			n	40	40	40	40	40	40	40	40	40	40	40	40	40
III	100	500														
			mean	12.57	40.13	59.65	81.05	99.30	117.25	131.62	148.45	157.55	171.85	183.93	189.78	203.30
			sd	3.05	5.92	8.14	10.37	12.57	13.68	15.42	17.40	19.56	18.45	18.71	20.58	19.79
			n	40	40	40	40	40	40	40	40	40	40	40	40	40
IV	200	500														
			mean	9.87	36.47	57.63	79.00	95.90	112.48	124.75	141.07	152.58	163.05	174.60	183.27	194.30
			sd	9.20	11.11	10.64	11.99	12.80	14.12	15.47	16.91	17.40	18.01	18.58	20.00	19.81
			n	40	40	40	40	40	40	40	40	40	40	40	40	40
V	200	1000														
			mean	9.45	35.65	56.53	76.10	92.77	107.65	119.57	135.07	144.73	155.38	167.65	177.53	188.08
			sd	4.12	6.24	8.52	10.70	12.66	14.55	15.07	15.83	15.81	16.30	16.66	17.82	18.90
			n	40	40	40	40	40	40	40	40	40	40	40	40	40

TABLE A-10
SUMMARY OF BODY WEIGHT GAINS (g) OF MALE RATS
(RECOVERY PERIOD)

GROUP	GRAPHITE mg/m³	PBL mg/m³		Study Day 96	103	110	117	124	131
I	0	0							
			mean	193.10	201.25	205.25	213.30	220.60	226.70
			sd	19.28	19.01	20.36	19.78	20.13	21.03
			n	20	20	20	20	20	20
II	100	250							
			mean	199.80	208.70	216.35	223.20	233.20	238.70
			sd	14.72	16.46	16.95	17.92	18.53	17.97
			n	20	20	20	20	20	20
III	100	500							
			mean	207.95	216.85	223.05	231.50	238.95	244.00
			sd	22.20	21.70	21.74	22.57	23.84	25.52
			n	20	20	20	20	20	20
IV	200	500							
			mean	204.75	214.60	221.35	230.00	237.10	243.80
			sd	20.00	20.80	21.49	23.18	24.92	23.74
			n	20	20	20	20	20	20
V	200	1000							
			mean	196.10	208.00	213.85	223.15	229.85	236.10
			sd	19.52	20.96	21.07	21.60	23.53	24.27
			n	20	20	20	20	20	20

TABLE A-11
SUMMARY OF AVERAGE DAILY FOOD CONSUMPTION (g) OF MALE RATS
(EXPOSURE PERIOD)

GROUP	GRAPHITE mg/m³	PBL mg/m³		Study Day 1-5	6-12	13-19	20-26	27-33	34-40	41-47	48-54	55-61	62-68	69-75	76-82	83-89
I	0	0														
			mean	19.06	19.06	20.07	21.48	21.94	20.88	21.24	20.87	20.82	21.07	20.85	19.47	19.38
			sd	1.57	1.49	1.52	1.77	1.57	1.61	0.90	1.43	1.47	1.82	1.21	1.37	2.01
			n	10	10	10	10	10	10	10	10	10	10	10	10	10
II	100	250														
			mean	18.99	18.77	20.82	21.33	22.31	20.51	21.36	21.81	21.85	20.98	20.71	20.12	21.14
			sd	1.83	1.18	1.68	1.84	2.11	2.00	1.31	1.25	1.11	1.22	1.40	1.19	1.02
			n	10	10	10	10	9[a]	9[a]	10	10	10	10	10	10	10
III	100	500														
			mean	18.58	19.04	20.97	21.01	20.88	20.56	20.05	20.97	20.86	21.45	21.14	20.25	19.81
			sd	1.31	1.36	1.62	1.83	1.59	1.77	1.46	1.68	1.92	2.45	1.75	1.33	1.63
			n	10	10	10	10	10	10	10	10	10	10	10	10	10
IV	200	500														
			mean	19.00	18.83	20.58	21.69	22.83	20.11	20.25	21.38	21.93	20.86	21.72	20.34	21.12
			sd	1.15	1.33	1.05	1.38	1.09	1.60	1.52	1.92	1.46	1.07	1.14	1.22	0.95
			n	10	10	10	10	10	10	10	10	10	10	10	10	10
V	200	1000														
			mean	17.65	18.11	19.83	20.87	21.44	19.79	19.82	21.55	20.73	20.70	19.24	20.08	20.42
			sd	2.58	2.10	2.23	2.39	2.05	2.46	2.27	2.16	1.58	2.39	1.86	1.79	2.11
			n	10	10	10	10	10	10	10	10	10	10	10	10	10

a Value for one rat excluded because it was inconsistent with other values for the same animal and inconsistent with body weight gain.

TABLE A-12
SUMMARY OF AVERAGE DAILY FOOD CONSUMPTION (g) OF MALE RATS
(RECOVERY PERIOD)

GROUP	GRAPHITE mg/m³	PBL mg/m³		Study Day 90-96	97-103	104-110	111-117	118-124	125-131
I	0	0							
			mean	18.62	19.84	19.23	20.64	20.17	19.20
			sd	2.12	1.29	1.22	1.52	1.55	1.62
			n	10	10	10	10	10	10
II	100	250							
			mean	20.97	22.44	22.74	23.16	22.89	22.20
			sd	1.55	1.66	1.13	1.26	1.73	1.20
			n	10	10	10	10	10	10
III	100	500							
			mean	20.36	21.92	23.17	22.61	22.70	21.92
			sd	1.30	1.39	1.53	1.43	1.09	1.27
			n	10	10	10	10	10	10
IV	200	500							
			mean	21.27	23.34	24.72	23.51	22.34	23.18
			sd	1.31	0.91	1.14	0.81	1.79	0.91
			n	10	10	10	10	10	10
V	200	1000							
			mean	20.64	21.99	23.83	22.79	22.44	21.70
			sd	1.90	2.01	1.97	1.42	1.39	1.80
			n	10	10	10	10	10	10

TABLE A-13
SUMMARY OF LUNG/BODY WEIGHT RATIOS OF MALE RATS

PERIOD	GROUP	GRAPHITE mg/m³	PBL mg/m³		LUNG WEIGHT/BODY WEIGHT (x 100)
Post-Exp	I	0	0		
				mean	0.63
				sd	0.14
				n	10
	II	100	250		
				mean	0.73
				sd	0.07
				n	10
	III	100	500		
				mean	0.82
				sd	0.08
				n	10
	IV	200	500		
				mean	0.87
				sd	0.07
				n	10
	V	200	1000		
				mean	0.85
				sd	0.05
				n	10
Post-Rec	I	0	0		
				mean	0.58
				sd	0.08
				n	10
	II	100	250		
				mean	0.70
				sd	0.06
				n	10
	III	100	500		
				mean	0.77
				sd	0.12
				n	10
	IV	200	500		
				mean	0.82
				sd	0.08
				n	10
	V	200	1000		
				mean	0.84
				sd	0.14
				n	10

TABLE A-14
SUMMARY OF CLINICAL CHEMISTRY TESTS OF MALE RATS
(PARAMETER SET A)

PERIOD	GROUP	GRAPHITE mg/m^3	PBL mg/m^3		CK	ALP	ALT	BUN	CREA	GLU	TP
Post-Exp	I	0	0								
				mean	137.60	300.60	83.40	15.83	0.64	189.61	7.12
				sd	53.11	32.67	39.33	1.75	0.08	34.76	0.23
				n	10	10	10	10	10	10	10
	II	100	250								
				mean	156.40	306.40	83.80	17.31	0.66	157.07	7.01
				sd	55.54	26.31	42.00	1.05	0.08	35.42	0.19
				n	10	10	10	10	10	10	10
	III	100	500								
				mean	164.50	299.00	55.10	15.62	0.64	173.52	7.14
				sd	82.62	30.92	12.96	1.37	0.06	33.43	0.30
				n	10	10	10	10	10	10	10
	IV	200	500								
				mean	225.90	300.40	85.40	17.29	0.69	178.98	6.81
				sd	135.63	27.81	48.56	1.62	0.14	40.79	0.26
				n	10	10	10	10	10	10	10
	V	200	1000								
				mean	95.20	300.50	53.20	16.76	0.62	172.90	6.81
				sd	22.79	26.51	7.15	1.38	0.06	53.07	0.13
				n	10	10	10	10	10	10	10
Post-Rec	I	0	0								
				mean	155.70	303.20	79.50	17.27	0.73	182.42	7.19
				sd	141.54	36.61	30.90	1.45	0.10	37.60	0.23
				n	10	10	10	10	10	10	10
	II	100	250								
				mean	122.10	310.80	74.20	17.50	0.66	165.84	7.21
				sd	59.34	22.05	28.70	1.39	0.08	23.02	0.25
				n	10	10	10	10	10	10	10
	III	100	500								
				mean	152.90	301.80	70.30	18.44	0.70	160.81	7.19
				sd	129.47	36.58	21.86	1.77	0.06	21.52	0.22
				n	10	10	10	10	10	10	10
	IV	200	500								
				mean	125.40	287.80	61.20	17.65	0.69	173.75	7.02
				sd	80.75	26.49	19.75	1.68	0.07	45.70	0.37
				n	10	10	10	10	10	10	10
	V	200	1000								
				mean	117.60	307.40	61.40	17.82	0.69	155.45	7.09
				sd	51.83	24.02	11.88	1.65	0.06	41.92	0.10
				n	10	10	10	10	10	10	10

CK = Creatine kinase (international units/liter serum)
ALP = Alkaline phosphatase (international units/liter serum)
ALT = Alanine aminotransferase (international units/liter serum)
BUN = Urea nitrogen (milligrams nitrogen/deciliter serum)
CREA = Creatinine (milligrams/deciliter serum)
GLU = Glucose (milligrams/deciliter serum)
TP = Total protein (grams protein/deciliter serum)

TABLE A-14
(Continued)
SUMMARY OF CLINICAL CHEMISTRY TESTS OF MALE RATS
(PARAMETER SET B)

PERIOD	GROUP	GRAPHITE mg/m^3	PBL mg/m^3		ALBG	CHOL	TRIG	CA	TBA	PHOS	SDH
Post-Exp	I	0	0								
				mean	4.27	43.76	183.78	12.13	21.81	9.52	56.51
				sd	0.12	2.77	29.63	0.52	8.21	1.31	55.95
				n	10	10	10	10	10	10	10
	II	100	250								
				mean	4.24	42.88	188.30	11.75	16.28	8.29	49.35
				sd	0.15	4.54	44.72	0.35	4.51	1.16	34.07
				n	10	10	10	10	10	10	10
	III	100	500								
				mean	4.29	41.06	176.61	12.03	15.18	8.64	26.85
				sd	0.16	2.19	27.39	0.30	2.10	0.67	11.51
				n	10	10	10	10	10	10	10
	IV	200	500								
				mean	4.17	38.21	180.52	11.59	20.09	8.52	61.52
				sd	0.13	3.95	24.24	0.28	10.69	1.02	54.49
				n	10	10	10	10	10	10	10
	V	200	1000								
				mean	4.12	38.33	178.04	11.66	14.64	9.01	24.69
				sd	0.15	2.58	42.70	0.41	2.86	1.32	7.27
				n	10	10	10	10	10	10	10
Post-Rec	I	0	0								
				mean	4.41	47.17	168.02	11.79	20.57	7.79	43.65
				sd	0.13	5.50	21.34	0.38	7.53	1.28	26.69
				n	10	10	10	10	10	10	10
	II	100	250								
				mean	4.34	45.77	171.68	11.88	15.79	7.05	38.58
				sd	0.15	3.53	18.66	0.23	3.98	0.68	22.93
				n	10	10	10	10	10	10	10
	III	100	500								
				mean	4.31	45.72	162.31	11.73	16.00	6.97	36.39
				sd	0.14	3.95	25.27	0.25	4.42	0.95	20.60
				n	10	10	10	10	10	10	10
	IV	200	500								
				mean	4.21	44.80	169.86	11.60	16.95	7.58	27.63
				sd	0.24	3.48	27.74	0.41	6.98	1.46	20.81
				n	10	10	10	10	10	10	10
	V	200	1000								
				mean	4.34	43.19	161.66	11.63	15.52	6.31	28.68
				sd	0.10	3.68	15.10	0.28	1.64	0.92	9.99
				n	10	10	10	10	10	10	10

ALBG = Albumin (grams/deciliter serum)
CHOL = Cholesterol (milligrams/deciliter serum)
TRIG = Triglycerides (milligrams/deciliter serum)
CA = Calcium (milligrams/deciliter serum)
PHOS = Inorganic phosphate (milligrams phosphate/deciliter serum)
SDH = Sorbitol dehydrogenase (international units/liter serum)
TBA = Total bile acids (micromoles/liter serum)

TABLE A-15
SUMMARY OF HEMATOLOGY TESTS OF MALE RATS

PERIOD	GROUP	GRAPHITE mg/m³	PBL mg/m³		WBC	RBC	HGB	HCT	MCV	MCH	MCHC	PLT
Post-Exp	I	0	0									
				mean	8.44	9.12	16.16	44.90	49.23	17.73	36.01	781.70
				sd	1.48	0.42	0.52	2.10	0.54	0.41	0.74	36.72
				n	10	10	10	10	10	10	10	10
	II	100	250									
				mean	8.38	9.01	15.78	44.30	49.17	17.53	35.64	782.20
				sd	1.56	0.39	0.51	1.97	0.56	0.39	0.76	51.27
				n	10	10	10	10	10	10	10	10
	III	100	500									
				mean	8.62	9.17	16.14	44.87	48.95	17.62	36.01	803.40
				sd	1.06	0.36	0.45	1.85	0.48	0.45	0.87	28.84
				n	10	10	10	10	10	10	10	10
	IV	200	500									
				mean	8.78	9.13	16.00	44.84	49.13	17.53	35.69	739.11
				sd	1.64	0.18	0.54	0.77	0.51	0.56	1.00	68.70
				n[a]	9	9	9	9	9	9	9	9
	V	200	1000									
				mean	9.67	8.85	15.61	43.36	49.03	17.66	36.02	769.10
				sd	0.98	0.46	0.64	2.00	0.38	0.33	0.62	34.66
				n	10	10	10	10	10	10	10	10
Post-Rec	I	0	0									
				mean	7.61	8.72	15.70	43.60	50.00	18.01	36.02	771.50
				sd	1.04	0.21	0.32	0.95	0.52	0.32	0.35	47.68
				n	10	10	10	10	10	10	10	10
	II	100	250									
				mean	8.75	8.89	15.87	44.15	49.65	17.86	35.96	773.80
				sd	0.87	0.37	0.50	1.72	0.52	0.41	0.64	39.28
				n	10	10	10	10	10	10	10	10
	III	100	500									
				mean	8.60	8.83	15.79	43.91	49.72	17.88	35.95	747.00
				sd	0.73	0.19	0.44	1.10	0.42	0.23	0.31	45.22
				n[a]	8	8	8	8	8	8	8	8
	IV	200	500									
				mean	9.31	8.63	15.49	42.96	49.76	17.94	36.08	793.89
				sd	1.25	0.38	0.64	1.80	0.37	0.17	0.35	56.61
				n[a]	9	9	9	9	9	9	9	9
	V	200	1000									
				mean	9.34	8.89	15.85	43.97	49.48	17.83	36.06	769.50
				sd	1.11	0.25	0.44	1.48	0.50	0.24	0.39	38.20
				n	10	10	10	10	10	10	10	10

a One (Group IV, Post-Exposure and Post-Recovery) or two (Group III Post-Recovery) clotted samples could not be analyzed.

WBC = White blood cell count (thousands of cells/cubic millimeter blood)
RBC = Red blood cell count (millions of cells/cubic millimeter blood)
HGB = Hemoglobin (grams/deciliter blood)
HCT = Hematocrit (percent)
MCV = Mean corpuscular volume (cubic microns)
MCH = Mean corpuscular hemoglobin (picograms)
MCHC = Mean corpuscular hemoglobin concentration (percent)
PLT = Platelet count (thousands of cells/cubic millimeter blood)

TABLE A-16
SUMMARY OF HEMATOLOGY WBC DIFFERENTIAL COUNTS OF MALE RATS

PERIOD	GROUP	GRAPHITE mg/m^3	PBL mg/m^3		WBC	NRBC	NEUT	LYMPH	MONO	EOS	BASO	IMNEUT
Post-Exp	I	0	0									
				mean	8.44	0.07	1.80	6.30	0.29	0.06	0.00	0.00
				sd	1.48	0.12	0.41	1.34	0.13	0.04	0.00	0.00
				n	10	10	10	10	10	10	10	10
	II	100	250									
				mean	8.38	0.02	2.02	6.04	0.27	0.05	0.00	0.00
				sd	1.56	0.05	0.63	1.15	0.12	0.05	0.00	0.00
				n	10	10	10	10	10	10	10	10
	III	100	500									
				mean	8.62	0.07	2.02	6.26	0.27	0.08	0.00	0.00
				sd	1.06	0.05	0.25	1.12	0.12	0.05	0.00	0.00
				n	10	10	10	10	10	10	10	10
	IV	200	500									
				mean	8.78	0.01	2.00	6.44	0.28	0.05	0.00	0.00
				sd	1.64	0.03	0.70	0.95	0.14	0.07	0.00	0.00
				n[a]	9	9	9	9	9	9	9	9
	V	200	1000									
				mean	9.67	0.03	2.22	6.99	0.39	0.08	0.00	0.00
				sd	0.98	0.04	0.38	0.82	0.11	0.07	0.00	0.00
				n	10	10	10	10	10	10	10	10
Post-Rec	I	0	0									
				mean	7.61	0.06	1.61	5.48	0.47	0.06	0.00	0.00
				sd	1.04	0.04	0.33	0.75	0.12	0.08	0.00	0.00
				n	10	10	10	10	10	10	10	10
	II	100	250									
				mean	8.75	0.06	2.11	6.04	0.52	0.09	0.00	0.00
				sd	0.87	0.06	0.33	0.60	0.20	0.07	0.00	0.00
				n	10	10	10	10	10	10	10	10
	III	100	500									
				mean	8.60	0.07	2.43	5.57	0.50	0.12	0.00	0.00
				sd	0.73	0.03	0.52	0.36	0.11	0.12	0.00	0.00
				n[a]	8	8	8	8	8	8	8	8
	IV	200	500									
				mean	9.31	0.03	2.62	6.00	0.63	0.06	0.00	0.00
				sd	1.25	0.04	0.40	1.12	0.15	0.05	0.00	0.00
				n[a]	9	9	9	9	9	9	9	9
	V	200	1000									
				mean	9.54	0.03	2.78	6.03	0.44	0.09	0.00	0.00
				sd	1.11	0.05	0.71	0.95	0.17	0.08	0.00	0.00
				n	10	10	10	10	10	10	10	10

a One (Group IV, Post-Exposure and Post-Recovery) or two (Group III Post-Recovery) clotted samples could not be analyzed.

WBC = White blood cell count (thousands of cells/cubic millimeter blood)
NRBC = Nucleated red blood cells (thousands of cells/cubic millimeter blood)
NEUT = Neutrophils (thousands of cells/cubic millimeter blood)
LYMPH = Lymphocytes (thousands of cells/cubic millimeter blood)
MONO = Monocytes (thousands of cells/cubic millimeter blood)
EOS = Eosinophils (thousands of cells/cubic millimeter blood)
BASO = Basophils (thousands of cells/cubic millimeter blood)
IMNEUT = Immature neutrophils (thousands of cells/cubic millimeter blood)

TABLE A-17
SUMMARY OF PULMONARY LAVAGE PARAMETERS IN MALE RATS

PERIOD	GROUP	GRAPHITE mg/m^3	PBL mg/m^3		TOTAL VIABLE CELLS $(\times 10^7)$	TOTAL CELLS $(\times 10^7)$	% VIABLE CELLS	% MACRO-PHAGES	% LYMPHO-CYTES	% NEUTRO-PHILS	% OTHER	LAVAGE FLUID PROTEIN (ug/ml)
Post-Exp	I	0	0									
				mean	2.24	2.26	98.64	99.70	0.30	0.00	0.00	177.97
				sd	0.75	0.75	2.24	0.67	0.67	0.00	0.00	63.59
				n	10	10	10	10	10	10	10	10
	II	100	250									
				mean	9.20	9.66	95.59	91.80	0.00	8.20	0.00	426.17
				sd	3.85	4.12	3.12	19.11	0.00	19.11	0.00	110.12
				n	10	10	10	10	10	10	10	10
	III	100	500									
				mean	8.19	8.74	93.57	92.70	0.00	7.30	0.00	483.50
				sd	1.30	1.27	3.63	16.14	0.00	16.14	0.00	143.89
				n	10	10	10	10	10	10	10	10
	IV	200	500									
				mean	10.04	10.93	92.75	73.90	0.50	25.60	0.00	523.00
				sd	2.10	2.71	4.90	22.85	1.27	22.01	0.00	88.40
				n	10	10	10	10	10	10	10	10
	V	200	1000									
				mean	9.26	10.02	92.87	88.30	0.00	11.70	0.00	501.64
				sd	2.26	2.62	2.67	12.20	0.00	12.20	0.00	71.58
				n	10	10	10	10	10	10	10	10
Post-Rec	I	0	0									
				mean	1.68	1.73	96.99	99.50	0.20	0.30	0.00	255.27
				sd	0.48	0.49	2.51	0.85	0.42	0.67	0.00	198.39
				n	10	10	10	10	10	10	10	10
	II	100	250									
				mean	7.27	7.70	94.84	77.10	0.00	22.90	0.00	463.59
				sd	1.44	1.67	2.49	10.48	0.00	10.48	0.00	173.79
				n	10	10	10	10	10	10	10	10
	III	100	500									
				mean	7.38	7.88	93.86	84.90	1.70	13.40	0.00	423.03
				sd	0.95	1.15	2.11	13.55	5.38	12.19	0.00	106.79
				n	10	10	10	10	10	10	10	10
	IV	200	500									
				mean	8.24	8.81	93.68	75.20	0.00	24.80	0.00	451.09
				sd	1.96	2.19	2.31	8.47	0.00	8.47	0.00	106.52
				n	10	10	10	10	10	10	10	10
	V	200	1000									
				mean	8.15	8.79	92.87	81.80	0.00	18.20	0.00	545.53
				sd	2.15	2.38	3.00	16.77	0.00	16.77	0.00	88.08
				n	10	10	10	10	10	10	10	10

TABLE A-18

LIST OF ABBREVIATIONS ACCORDING TO SUBJECT AREAS

Experimental Design

PBL	-	petroleum-based liquid
EXP	-	post-exposure
REC	-	post-recovery
LAV	-	designated for pulmonary lavage
PATH	-	designated for pathology, clinical pathology and (recovery rats only) food consumption
PF	-	designated for pulmonary function tests

Lung Weight

LUNG/BW	-	lung to body weight ratio (x 100)

Clinical Chemistry

CK	-	creatine kinase (international units/liter serum)
ALP	-	alkaline phosphatase (international units/liter serum)
ALT	-	alanine aminotransferase (international units/liter serum)
BUN	-	urea nitrogen (milligrams nitrogen/deciliter serum)
CREA	-	creatinine (milligrams/deciliter serum)
GLU	-	glucose (milligrams/deciliter serum)
TP	-	total protein (grams protein/deciliter serum)
ALBG	-	albumin (grams/deciliter serum)
CHOL	-	cholesterol (milligrams/deciliter serum)
TRIG	-	triglycerides (milligrams/deciliter serum)
CA	-	calcium (milligrams/deciliter serum)
PHOS	-	inorganic phosphate (milligrams phosphate/deciliter serum)
SDH	-	sorbitol dehydrogenase (international units/liter serum)
TBA	-	total bile acids (micromoles/liter serum)

Hematology

WBC	-	white blood cell count (thousands of cells/cubic millimeter blood)
RBC	-	red blood cell count (millions of cells/cubic millimeter blood)
HGB	-	hemoglobin (grams/deciliter blood)
HCT	-	hematocrit (percent)
MCV	-	mean corpuscular volume (cubic microns)
MCH	-	mean corpuscular hemoglobin (picograms)
MCHC	-	mean corpuscular hemoglobin concentration (percent)
PLT	-	platelet count (thousands of cells/cubic millimeter blood)

TABLE A-18
(Continued)

Hematology Differential Count

WBC	-	white blood cell count (thousands of cells/cubic millimeter blood = thsn/cmm)
NRBC	-	nucleated red blood cells (thsn/cmm)
NEUT	-	neutrophils (thsn/cmm)
LYMPH	-	lymphocytes (thsn/cmm)
MONO	-	monocytes (thsn/cmm)
EOSIN	-	eosinophils (thsn/cmm)
BASO	-	basophils (thsn/cmm)
IMNEUT	-	immature neutrophils (thsn/cmm)

Pulmonary Function

TLC	-	total lung capacity (ml)
RV	-	residual volume (ml)
DLCO	-	diffusion capacity for carbon monoxide (ml/min*torr)
VCGAS	-	vital capacity (ml)(gas dilution-derived)
VCPV	-	vital capacity (pressure-volume derived) (ml)
CPK	-	peak compliance (ml/cm H_2O)
CCHORD	-	compliance (tangent) at 0 to 10 cm H_2O (ml/cm H_2O)
FVC	-	forced vital capacity (ml)
FEV50	-	forced expiratory volume at 50 msec of expiration (ml @ 50 msec)
FEV100	-	forced expiratory volume at 100 msec of expiration (ml @ 100 msec)
FEV200	-	forced expiratory volume at 200 msec of expiration (ml @ 200 msec)
FEV400	-	forced expiratory volume at 400 msec of expiration (ml @ 400 msec)
PEF	-	peak expiratory flow (ml/sec)
MMEF	-	mean mid-expiratory flow (ml/sec)
VPEF	-	volume at PEF (ml)
FEF75	-	forced expiratory flow at 75% of remaining FVC (ml/sec)
FEF50	-	forced expiratory flow at 50% of remaining FVC (ml/sec)
FEF25	-	forced expiratory flow at 25% of remaining FVC (ml/sec)
FEF10	-	forced expiratory flow at 10% of remaining FVC (ml/sec)
EEV	-	end expiratory volume (ml)

PART ONE

APPENDIX B

PATHOLOGY REPORT

FINAL PATHOLOGY REPORT
FOR

THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS

IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

PREPARED
BY
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PATHOLOGY NARRATIVE

FINAL PATHOLOGY REPORT

THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS

INTRODUCTION

This report by Pathology Associates, Inc. (PAI) to IIT Research Institute (IITRI), 10 West 35th Street, Chicago, Illinois, 60616-3799, presents the results of pathology support for IITRI Project Number L06234, Study Number 3.

EXPERIMENTAL DESIGN AND METHODS

This study used one hundred male F344/N rats which were divided into ten groups of ten animals each (see Attachment 1, Summary of Experimental Design). Each group was exposed by whole body inhalation to filtered air (negative control) or a combination of petroleum-based liquid (fog oil) and graphite. Exposures were 4 hours/day, 4 days/week for 13 weeks. At the conclusion of the exposure period, fifty animals (post-exposure study) were killed via asphyxiation with carbon dioxide and subjected to a complete necropsy. The remaining fifty animals (recovery study) were allowed a 6 week recovery period following the last exposure before being killed and necropsied.

All protocol required tissues (see Attachment 2) were preserved in 10% neutral buffered formalin. After thorough fixation, all protocol required tissues from animals in the post-exposure and recovery studies were processed, embedded in paraffin, sectioned at approximately 5 μm and stained with hematoxylin and eosin (H&E). These tissues were then examined microscopically. Bronchial lymph nodes were taken as pulmonary lymph nodes. Mediastinal lymph nodes were collected and examined only if they contained a gross lesion.

Microscopic findings for all groups examined are summarized in the Project Summary Tables (Section II). The mean group severity scores, determined by dividing the sum of all severity scores for a finding by the number of tissues examined, are found in the Severity Summary Tables (Section III). Microscopic diagnoses for protocol required tissues for individual animals are presented in the Tabulated Animal Data Table (Section IV). Microscopic

diagnoses are correlated with gross lesions, when possible, in the Correlation of Gross and Microscopic (Micro) Findings Table (Section V). The codes used as entries in these tables are explained in the Reports Code Table (Attachment 4). Abbreviations used in the tables are explained in the Abbreviation List (Attachment 5).

RESULTS

Gross Lesions

Observations at necropsy which were associated with exposure to graphite-fog oil combinations were size and color changes in lungs and lymph nodes (pulmonary and mediastinal lymph nodes). These are summarized in the Summary of Gross Lesions (Attachment 3). Gray to black discoloration in lungs and lympn nodes was attributed to exposure to graphite. Enlarged lymph nodes were associated with lymphoid hyperplasia and increased, graphite-laden, macrophages.

Diagnostic Terms

Morphologic features of terms which follow are presented to aid in interpreting data in the tables. The terms listed here were not necessarily associated with the test article.

Nose

Hyperplasia of goblet cells refers to an increase in number of mucus-producing goblet cells in the respiratory epithelium.

Lymph Nodes

Hyperplasia of lymph nodes was characterized by enlargement due to increased numbers of lymphocytes and plasma cells. Germinal centers were increased in size and number. Granulomas were foci of large activated macrophages (histiocytes) which contained abundant pale cytoplasm and a single, usually reniform nucleus. Granulomas occurred in bronchial and mediastinal lymph nodes and within peribronchiolar lymphoid tissue in the lung. They did not contain multinucleated giant cells, but did contain graphite pigment.

Lung

Epithelial hyperplasia in the lung occurred in alveoli and terminal bronchioles. Hyperplastic alveolar epithelial cells were enlarged, with abundant pale or vacuolated cytoplasm. They had a generally oval to rectangular shape and oval nucleus. Hyperplasia of epithelium in terminal bronchioles consisted of crowded, enlarged epithelial cells. Epithelial hyperplasia in terminal bronchioles was often associated with clusters of graphite-laden macrophages. Granulomatous inflammation in the lung was characterized by aggregates of activated macrophages containing graphite. These were randomly distributed in the lung and were

found in alveoli. Perivascular inflammation was used to describe areas of inflammation composed of macrophages, lymphocytes, and neutrophils. These varied from very small to large, and generally had a perivascular distribution. The infiltrates tended to extend into adjacent alveolar walls and spaces. In these areas, the alveolar epithelium was slightly hyperplastic.

Pigment

Pigment was a granular black material seen within macrophages in alveoli, interstitium, and lymphoid tissue of the lung or in mediastinal or bronchial lymph nodes. It occurred only in groups receiving graphite. Its appearance is typical of graphite, and it was interpreted as graphite.

Kidney

Hyaline droplets were small to large homogeneous eosinophilic droplets in the cytoplasm of proximal tubular epithelium. Some were very large and appeared to have been intratubular rather than intracytoplasmic.

The remainder of the diagnoses used in this study were considered to be self-explanatory, and were not discussed in this section.

Histopathology

Hyperplasia of goblet cells occurred in the respiratory epithelium of the nasal septum in the first and second nasal sections and in the pharyngeal duct in the third nasal section. It did not occur in negative control animals in either the post-exposure or recovery studies. The incidence of goblet cell hyperplasia was similar in all groups exposed to graphite and fog oil in both post-exposure and recovery studies. Resolution of this change appeared to have begun during the recovery period, as mean group severity scores decreased by more than fifty percent between the post-exposure and recovery sacrifices. For these reasons, hyperplasia of goblet cells in the respiratory epithelium of the nose was interpreted as a test article related effect that was undergoing resolution.

Pigment was not seen in animals exposed to filtered air (negative control). Pigment was seen in the lung of all animals exposed to all four graphite-fog oil combinations. Within each of the four exposure groups, incidence and severity of pigment in the lung were similar at the end of the exposures (post-exposure study), and at the end of the recovery period (recovery study). Pigment occurred within macrophages in alveoli, interstitium, and lymphoid tissue in the lung. It appeared to be inert in these locations. Pigment was also seen in macrophages forming microgranulomas in the alveoli and lymphoid tissue of the lung. Pigment was observed in sinusoids and in granulomas in pulmonary and mediastinal lymph nodes in the post-exposure and recovery studies. These

observations are consistent with normal clearance of inert particulate materials from the lung. Alveolar macrophages phagocytize the particles and either move up the airways with mucus to be expectorated, or move into lymphatics of the interstitium and then into medullary sinuses of the draining lymph nodes. When the rate of exposure to inert materials exceeds the rate at which they can be cleared from the lung, the materials will accumulate in foreign-body granulomas. This has occurred in both the post-exposure and recovery studies. The observation that incidence and severity of pigment deposition had not decreased by the end of the recovery period suggests that the clearance mechanism of the lung was still overloaded after a 6 week recovery period. For these reasons, the presence of pigment in these locations is interpreted as evidence of exposure to graphite, but not as a test article related lesion.

Hyperplasia of epithelium in the lung occurred in alveoli and in terminal bronchioles. This change did not occur in negative control animals, but did occur in all four treatment groups in both the post-exposure and recovery studies. The incidence of epithelial hyperplasia in the lung was 100% in all treatment groups in the post-exposure and recovery studies. In each exposure group, the mean group severity scores of epithelial hyperplasia in the lungs were similar at the end of exposure and at the end of the recovery period. The lack of resolution of this change may have resulted from the persistence of graphite pigment during the recovery period. For these reasons, this change was interpreted as test article related.

The incidence of perivascular inflammation in the lung of negative control animals was 90% at the end of exposure and after the recovery period. The incidence in animals exposed to the combinations of fog oil and graphite was varied but was generally lower than in the control groups. This may have been a real difference but the large amount of pigment, granulomatous inflammation, and epithelial hyperplasia probably masked this change to some degree. The occurrence of perivascular inflammation in negative control animals and its histologic character and distribution also suggest this lesion is a response to an unknown infectious or toxic agent. Similar lesions have been observed in other studies in this and other laboratories, but no causative agent has been proven. This lesion was not considered test article related.

Hyperplasia and granulomas did not occur in pulmonary lymph nodes or in lymphoid tissues of the lung in the negative control groups in the post-exposure or recovery studies. These changes did occur in pulmonary and mediastinal lymph nodes and in lymphoid tissues of the lung in all other exposure groups in the post-exposure and recovery studies. Hyperplasia of lung-associated lymph nodes and lymphoid tissues is commonly associated with inflammation in the lung. In spite of the occurrence of perivascular inflammation in the lung of 90% of the negative control animals in the post-exposure and recovery studies, these animals did not have

hyperplasia of these lymphoid tissues. Hyperplasia of these lymphoid tissues did occur in all groups exposed to graphite-fog oil combinations, with an incidence of 80-100% in all groups. For these reasons, hyperplasia of pulmonary and mediastinal lymph nodes and of lymphoid tissue within the lung was interpreted as associated with exposure to graphite-fog oil combinations.

Granulomas, in conjunction with graphite pigment, occurred in the pulmonary and mediastinal lymph nodes and within the lymphoid tissues of the lung in 70-100% of animals exposed to graphite in the post-exposure and recovery studies. They did not occur in any negative control animals. These granulomas contained graphite and were interpreted as representing the normal clearance mechanism for inert particles such as graphite. For these reasons, the presence of granulomas in pulmonary and mediastinal lymph nodes and in lymphoid tissues in the lung were interpreted as not test article related.

Hyaline droplets occurred in the proximal convoluted tubules of the kidney in all animals in the post-exposure and recovery studies. Hyaline droplets represent resorbed alpha$_{2u}$globulin, which is excreted in large amount by the kidney of mature male rats. This creates a physiologic proteinuria which does not occur in mature female rats or in other species. The presence of hyaline droplets in the kidney of male rats can be accentuated by volatile hydrocarbons, and in some cases can be associated with a nephropathy. Mean group severity scores for hyaline droplets in post-exposure animals were 1.5 to 2.4 times higher than mean group severity scores for hyaline droplets in corresponding exposure groups in the recovery study. The incidence and severity of hyaline droplet formation in all recovery study animals that had been exposed to graphite-fog oil combinations were similar to the incidence and severity of hyaline droplet formation in negative control animals. For these reasons, exposure of animals to graphite-fog oil combinations was interpreted as associated with an increase in hyaline droplet formation in the kidney.

Other lesions occurring in respiratory tract tissues such as nose, larynx, or trachea were of low and sporadic incidence. They were not considered test article related changes. Lesions in other organs such as cardiomyopathy, urinary bladder calculi, and cellular infiltrates in the kidney were considered incidental spontaneous lesions not related to test articles.

CONCLUSIONS

Under the conditions of this study, exposure of animals to graphite-fog oil combinations was associated with reversible hyperplasia of goblet cells in the respiratory epithelium of the nose. Animals exposed to graphite-fog oil combinations also developed hyperplasia of epithelium in the lung, hyperplasia of lymphoid tissue in the lung, and draining lymph nodes. These

changes did not resolve during the recovery period. Hyaline droplet formation in the proximal convoluted tubule of the kidney was exacerbated by exposure to the graphite-fog oil combinations, but had decreased to post-exposure negative control levels by the end of the recovery period. Perivascular inflammation in the lungs occurred in post-exposure and recovery study animals including negative control and all treatment groups. This change suggested a response to an infectious or toxic agent, but was not a test article related change.

Michael J. Tomlinson, DVM, PhD
Diplomate ACVP

12-10-92
Date

ATTACHMENT 1

SUMMARY OF EXPERIMENTAL DESIGN

SUMMARY OF EXPERIMENTAL DESIGN

Test Group	Concentration in mg/m^3 of Fog Oil	Graphite	Number of Animals[1] Post-Exposure Study	Recovery Study
I	0	0	10	10
II	250	100	10	10
III	500	100	10	10
IV	500	200	10	10
V	1000	200	10	10

1: All animals were male F344/N rats

Exposures were for 4 hours/day, 4 days/week for 13 weeks; recovery period was 6 weeks.

ATTACHMENT 2

PROTOCOL-REQUIRED TISSUES

PROTOCOL REQUIRED TISSUES

Salivary Gland (Mandibular)
Mammary Gland
*Thymus
*Heart
*Lung
*Trachea
*Pulmonary Lymph Nodes (Bronchial)
*Liver
*Spleen
Seminal Vesicles
*Stomach
*Adrenal Glands
Sciatic Nerve
*Brain
Eyes
Spinal Cord
*Skin
*Gross Lesions
Animal Identification
Lymph Nodes (Submandibular)
*Sternum
Thyroid
Parathyroid
*Esophagus
Testes
Prostate
*Urinary Bladder
Duodenum
Ileum
Colon
Jejunum
Cecum
Mesenteric Lymph Node
*Kidney
Skeletal Muscle
Pituitary
*Larynx
*Nasal Turbinates

All protocol required tissues were collected and placed in fixative (10% neutral buffered formalin) at necropsy. Those marked with an asterisk (*) were processed into slides and evaluated by light microscopy for all groups in the post-exposure and recovery studies.

ATTACHMENT 3

SUMMARY OF GROSS LESIONS

SUMMARY OF GROSS LESIONS

Number of Animals with Lesion

Test Group	Number of Animals per Group	LN, Bronchial		LN, Mediastinal		Lung
		Enlargement	Color Change	Enlargement	Color Change	Color Change
I	10	0	0	0	0	0
I-R	10	0	0	0	0	0
II	10	10	10	10	10	10
II-R	10	9	9	10	10	10
III	10	10	10	10	10	10
III-R	10	10	10	10	10	10
IV	10	9	9	10	10	10
IV-R	10	10	10	10	10	10
V	10	9	9	10	9	10
V-R	10	10	10	10	10	10

ATTACHMENT 4

REPORTS CODE TABLE

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Reports Code Table

N	Tissues within normal histological limits
A	Autolysis precluding adequate evaluation
P	Paired organ missing
U	Tissues unsuitable for complete evaluation
S	Tissues not applicable to animal
*	Tissues not required by protocol

1	minimal
2	mild
3	moderate
4	marked
)	focal
]	locally extensive
>	multifocal
P	Present
B	Neoplasm, Benign
M	Neoplasm, Malignant without Metastasis
C	Neoplasm, Malignant with Metastasis
X	Metastatic Site (+)
-	No data entered

ATTACHMENT 5

ABBREVIATION LIST

HISTOPATHOLOGY TABLES

ABBREVIATION LIST

CELL - CELLULAR
CYTO - CYTOPLASM
EPITH - EPITHELIUM
INFILT - INFILTRATE
LN - LYMPH NODE
VACUOL - VACUOLIZATION

SECTION II

PROJECT SUMMARY TABLE

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L062343 FATES: SCHEDULED SACRIFICE
DAYS : 89 SEX: MALE

GROUP:	I	II	III	IV	V
NUMBER OF ANIMALS:	10	10	10	10	10

		#	%	#	%	#	%	#	%	#	%
NOSE	# Ex	10		10		10		10		10	
Hyperplasia,goblet cell		0	(0)	10	(100)	10	(100)	10	(100)	9	(90)
Nasolacrimal duct,cell infilt		1	(10)	1	(10)	0	(0)	0	(0)	0	(0)
Nasolacrimal duct,hemorrhage		4	(40)	2	(20)	1	(10)	0	(0)	2	(20)
Nasolacrimal duct,hyperplasia		0	(0)	1	(10)	0	(0)	0	(0)	1	(10)
Septum,cellular infiltrate		0	(0)	1	(10)	0	(0)	0	(0)	0	(0)
Inflammation		0	(0)	1	(10)	0	(0)	0	(0)	0	(0)
Pigment		0	(0)	1	(10)	0	(0)	0	(0)	0	(0)
Epithelium,hyperplasia		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
LARYNX	# Ex	8		10		10		10		10	
Glands,cellular infiltrate		1	(13)	0	(0)	0	(0)	0	(0)	0	(0)
Lumen,mucus		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
Respiratory epith,cell infilt		2	(25)	0	(0)	1	(10)	0	(0)	0	(0)
Respiratory epith,hyperplasia		0	(0)	2	(20)	0	(0)	0	(0)	1	(10)
TRACHEA	# Ex	10		10		10		10		10	
Epithelium,cellular infilt		1	(10)	0	(0)	0	(0)	0	(0)	0	(0)
Epithelium,hyperplasia		0	(0)	0	(0)	0	(0)	0	(0)	3	(30)
Epithelium,pigment		0	(0)	0	(0)	0	(0)	0	(0)	2	(20)
ESOPHAGUS	# Ex	10		10		10		10		10	
PULMONARY LN	# Ex	8		9		10		9		10	
Granuloma		0	(0)	9	(100)	10	(100)	9	(100)	10	(100)
Hyperplasia		0	(0)	9	(100)	10	(100)	9	(100)	10	(100)
Pigment		0	(0)	9	(100)	10	(100)	9	(100)	10	(100)
LUNG	# Ex	10		10		10		10		10	
Epithelium,hyperplasia		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
Hemorrhage		2	(20)	0	(0)	0	(0)	0	(0)	0	(0)
Inflammation,granulomatous		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
Inflammation,perivascular		9	(90)	1	(10)	8	(80)	6	(60)	1	(10)
Lymphoid tissue,granuloma		0	(0)	9	(90)	10	(100)	9	(90)	7	(70)
Lymphoid tissue,hyperplasia		0	(0)	10	(100)	10	(100)	9	(90)	8	(80)
Pigment		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L062343 FATES: SCHEDULED SACRIFICE
DAYS : 89 SEX: MALE

GROUP:		I		II		III		IV		V	
NUMBER OF ANIMALS:		10		10		10		10		10	
		#	%	#	%	#	%	#	%	#	%
HEART	# Ex	10		10		10		10		10	
Cardiomyopathy		8	(80)	8	(80)	4	(40)	7	(70)	6	(60)
URINARY BLADDER	# Ex	10		10		10		10		10	
STOMACH	# Ex	10		10		10		10		10	
Forestomach,epith,hyperplasia		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
LIVER	# Ex	10		10		10		10		10	
Cellular infiltrate,periportal		0	(0)	0	(0)	1	(10)	0	(0)	1	(10)
Hepatocyte,necrosis		4	(40)	2	(20)	2	(20)	1	(10)	4	(40)
Hepatocyte,vacuol,cyto		1	(10)	1	(10)	0	(0)	2	(20)	2	(20)
Hepatodiaphragmatic nodule		2	(20)	1	(10)	0	(0)	0	(0)	1	(10)
SPLEEN	# Ex	10		10		10		10		10	
SKIN	# Ex	9		10		10		10		10	
KIDNEY	# Ex	10		10		10		10		10	
Cortex,cellular infiltrate		0	(0)	0	(0)	3	(30)	2	(20)	0	(0)
Hyaline droplets		10	(100)	10	(100)	10	(100)	10	(100)	10	(100)
Renal tubule,casts,protein		2	(20)	0	(0)	0	(0)	0	(0)	1	(10)
Renal tubule,mineralization		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
Renal tubule,regeneration		2	(20)	0	(0)	1	(10)	3	(30)	0	(0)
ADRENALS	# Ex	10		10		10		10		10	
THYMUS	# Ex	10		10		10		10		10	
BRAIN	# Ex	10		10		10		10		10	

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L062343 FATES: SCHEDULED SACRIFICE
DAYS : 89 SEX: MALE

GROUP:		I		II		III		IV		V	
NUMBER OF ANIMALS:		10		10		10		10		10	
		#	%	#	%	#	%	#	%	#	%
STERNUM	# Ex	10		10		10		10		10	

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L062343
DAYS : 89
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:	I	II	III	IV	V
NUMBER OF ANIMALS:	10	10	10	10	10

OTHER TISSUES AND LESIONS:	#	%	#	%	#	%	#	%	#	%
MEDIASTINAL LN: Granuloma	0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
MEDIASTINAL LN: Hyperplasia	0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
MEDIASTINAL LN: Pigment	0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
MESENTERY: LN, congestion	1	(10)	0	(0)	0	(0)	0	(0)	0	(0)
TISSUE NOS: Fat, necrosis	1	(10)	0	(0)	0	(0)	0	(0)	0	(0)

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L62343R
DAYS : 131
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:	I-R	II-R	III-R	IV-R	V-R
NUMBER OF ANIMALS:	10	10	10	10	10

		#	%	#	%	#	%	#	%	#	%
NOSE	# Ex	10		10		10		10		10	
Hyperplasia,goblet cell		0	(0)	9	(90)	8	(80)	10	(100)	10	(100)
Nasolacrimal duct,hemorrhage		4	(40)	0	(0)	1	(10)	4	(40)	0	(0)
Nasolacrimal duct,hyperplasia		0	(0)	1	(10)	0	(0)	1	(10)	0	(0)
Hemorrhage		0	(0)	0	(0)	1	(10)	0	(0)	0	(0)
LARYNX	# Ex	10		10		10		10		10	
Respiratory epith,cell infilt		2	(20)	3	(30)	1	(10)	0	(0)	1	(10)
Respiratory epith,hyperplasia		0	(0)	0	(0)	0	(0)	1	(10)	0	(0)
TRACHEA	# Ex	10		10		10		10		10	
ESOPHAGUS	# Ex	10		10		10		10		10	
PULMONARY LN	# Ex	5		8		10		10		10	
Granuloma		0	(0)	8	(100)	10	(100)	10	(100)	10	(100)
Hyperplasia		0	(0)	8	(100)	10	(100)	10	(100)	10	(100)
Pigment		0	(0)	8	(100)	10	(100)	10	(100)	10	(100)
Pigment,refractile		1	(20)	0	(0)	0	(0)	0	(0)	0	(0)
LUNG	# Ex	10		10		10		10		10	
Alveolus,mineralization		1	(10)	0	(0)	0	(0)	0	(0)	0	(0)
Epithelium,hyperplasia		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
Hemorrhage		1	(10)	0	(0)	0	(0)	0	(0)	0	(0)
Inflammation,granulomatous		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
Inflammation,perivascular		9	(90)	6	(60)	5	(50)	7	(70)	4	(40)
Lymphoid tissue,granuloma		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
Lymphoid tissue,hyperplasia		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
Pigment		0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
HEART	# Ex	10		10		10		10		10	
Cardiomyopathy		5	(50)	7	(70)	8	(80)	5	(50)	10	(100)

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THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L62343R
DAYS : 131
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:	I-R	II-R	III-R	IV-R	V-R
NUMBER OF ANIMALS:	10	10	10	10	10

		#	%	#	%	#	%	#	%	#	%
URINARY BLADDER	# Ex	10		10		10		10		10	
Transitional epith,cell infilt		0	(0)	1	(10)	0	(0)	0	(0)	1	(10)
Calculus,micro observation		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
Mineralization		0	(0)	0	(0)	0	(0)	1	(10)	0	(0)
STOMACH	# Ex	10		10		10		10		10	
LIVER	# Ex	10		10		10		10		10	
Cellular infiltrate,periportal		0	(0)	2	(20)	1	(10)	3	(30)	2	(20)
Hepatocyte,necrosis		1	(10)	5	(50)	6	(60)	3	(30)	7	(70)
Hepatocyte,vacuol,cyto		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
Hepatodiaphragmatic nodule		0	(0)	0	(0)	0	(0)	0	(0)	1	(10)
SPLEEN	# Ex	10		10		10		10		10	
SKIN	# Ex	10		10		10		10		10	
KIDNEY	# Ex	10		10		10		10		10	
Cortex,cellular infiltrate		0	(0)	1	(10)	0	(0)	1	(10)	0	(0)
Hyaline droplets		10	(100)	10	(100)	10	(100)	10	(100)	10	(100)
Renal tubule,casts,protein		2	(20)	0	(0)	0	(0)	0	(0)	0	(0)
Renal tubule,regeneration		4	(40)	0	(0)	2	(20)	3	(30)	0	(0)
ADRENALS	# Ex	10		10		10		10		10	
THYMUS	# Ex	10		10		10		10		10	
BRAIN	# Ex	10		10		10		10		10	
STERNUM	# Ex	9		10		10		10		10	

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Project Summary Table

SUMMARY: Incidence of NON-NEOPLASTIC Microscopic Findings

PROJECT ID. NO: L62343R
DAYS : 131
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:	I-R	II-R	III-R	IV-R	V-R
NUMBER OF ANIMALS:	10	10	10	10	10

	#	%	#	%	#	%	#	%	#	%
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN - Granuloma	0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
MEDIASTINAL LN - Hyperplasia	0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
MEDIASTINAL LN - Pigment	0	(0)	10	(100)	10	(100)	10	(100)	10	(100)
EYE - Cataract	0	(0)	0	(0)	1	(10)	0	(0)	0	(0)

SECTION III

SEVERITY SUMMARY TABLE

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Severity Summary Table

PROJECT ID. NO: L062343 FATES: SCHEDULED SACRIFICE
DAYS: 89 SEX: MALE

GROUP:		I		II		III		IV		V	
NUMBER OF ANIMALS:		10		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV	#	SEV
NOSE	# Ex	10		10		10		10		10	
Hyperplasia,goblet cell		0		10	2.80	10	2.50	10	3.00	9	2.50
Nasolacrimal duct,cell infilt		1	0.20	1	0.30	0		0		0	
Nasolacrimal duct,hemorrhage		4	0.40	2	0.20	1	0.10	0		2	0.20
Nasolacrimal duct,hyperplasia		0		1	0.10	0		0		1	0.10
Septum,cellular infiltrate		0		1	0.10	0		0		0	
Inflammation		0		1	0.20	0		0		0	
Pigment		0		1	0.10	0		0		0	
Epithelium,hyperplasia		0		0		0		0		1	0.20
LARYNX	# Ex	8		10		10		10		10	
Glands,cellular infiltrate		1	0.13	0		0		0		0	
Lumen,mucus		0		0		0		0		1	0.30
Respiratory epith,cell infilt		2	0.25	0		1	0.20	0		0	
Respiratory epith,hyperplasia		0		2	0.20	0		0		1	0.10
TRACHEA	# Ex	10		10		10		10		10	
Epithelium,cellular infilt		1	0.10	0		0		0		0	
Epithelium,hyperplasia		0		0		0		0		3	0.30
Epithelium,pigment		0		0		0		0		2	0.20
ESOPHAGUS	# Ex	10		10		10		10		10	
PULMONARY LN	# Ex	8		9		10		9		10	
Granuloma		0		9	2.44	10	2.10	9	2.11	10	3.10
Hyperplasia		0		9	3.11	10	2.80	9	2.78	10	3.60
Pigment		0		9	1.67	10	1.00	9	1.78	10	2.10
LUNG	# Ex	10		10		10		10		10	
Epithelium,hyperplasia		0		10	2.70	10	2.50	10	3.20	10	3.30
Hemorrhage		2	0.20	0		0		0		0	
Inflammation,granulomatous		0		10	2.10	10	2.20	10	3.00	10	3.10
Inflammation,perivascular		9	1.50	1	0.10	8	1.30	6	0.80	1	0.10
Lymphoid tissue,granuloma		0		9	2.10	10	1.90	9	2.00	7	1.70
Lymphoid tissue,hyperplasia		0		10	2.30	10	2.10	9	2.10	8	2.50

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Severity Summary Table

PROJECT ID. NO: L062343
DAYS: 89
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:		I		II		III		IV		V	
NUMBER OF ANIMALS:		10		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV	#	SEV
Pigment		0		10	2.60	10	2.90	10	3.50	10	4.00
HEART	# Ex	10		10		10		10		10	
Cardiomyopathy		8	1.00	8	0.90	4	0.50	7	0.70	6	0.60
URINARY BLADDER	# Ex	10		10		10		10		10	
STOMACH	# Ex	10		10		10		10		10	
Forestomach,epith,hyperplasia		0		0		0		0		1	0.10
LIVER	# Ex	10		10		10		10		10	
Cellular infiltrate,periportal		0		0		1	0.10	0		1	0.10
Hepatocyte,necrosis		4	0.50	2	0.20	2	0.20	1	0.10	4	0.40
Hepatocyte,vacuol,cyto		1	0.20	1	0.10	0		2	0.30	2	0.20
Hepatodiaphragmatic nodule		2	0.30	1	0.10	0		0		1	0.10
SPLEEN	# Ex	10		10		10		10		10	
SKIN	# Ex	9		10		10		10		10	
KIDNEY	# Ex	10		10		10		10		10	
Cortex,cellular infiltrate		0		0		3	0.30	2	0.30	0	
Hyaline droplets		10	1.60	10	2.20	10	2.00	10	2.40	10	2.40
Renal tubule,casts,protein		2	0.20	0		0		0		1	0.10
Renal tubule,mineralization		0		0		0		0		1	0.10
Renal tubule,regeneration		2	0.20	0		1	0.10	3	0.30	0	
ADRENALS	# Ex	10		10		10		10		10	
THYMUS	# Ex	10		10		10		10		10	

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Severity Summary Table

PROJECT ID. NO: L062343 FATES: SCHEDULED SACRIFICE
DAYS: 89 SEX: MALE

GROUP:		I	II	III	IV	V
NUMBER OF ANIMALS:		10	10	10	10	10
		# SEV	# SEV	# SEV	# SEV	# SEV
BRAIN	# Ex	10	10	10	10	10
STERNUM	# Ex	10	10	10	10	10

* Severity calculated by the number of tissues examined.

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Severity Summary Table

PROJECT ID. NO: L62343R
DAYS: 131
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:		I-R		II-R		III-R		IV-R		V-R	
NUMBER OF ANIMALS:		10		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV	#	SEV
NOSE	# Ex	10		10		10		10		10	
Hyperplasia,goblet cell		0		9	1.20	8	1.00	10	1.00	10	1.20
Nasolacrimal duct,hemorrhage		4	0.40	0		1	0.10	4	0.40	0	
Nasolacrimal duct,hyperplasia		0		1	0.10	0		1	0.10	0	
Hemorrhage		0		0		1	0.20	0		0	
LARYNX	# Ex	10		10		10		10		10	
Respiratory epith,cell infilt		2	0.20	3	0.30	1	0.20	0		1	0.10
Respiratory epith,hyperplasia		0		0		0		1	0.10	0	
TRACHEA	# Ex	10		10		10		10		10	
ESOPHAGUS	# Ex	10		10		10		10		10	
PULMONARY LN	# Ex	5		8		10		10		10	
Granuloma		0		8	2.38	10	2.50	10	2.60	10	3.20
Hyperplasia		0		8	2.88	10	3.40	10	2.80	10	3.40
Pigment		0		8	2.00	10	1.90	10	2.10	10	2.40
Pigment,refractile		1	0.20	0		0		0		0	
LUNG	# Ex	10		10		10		10		10	
Alveolus,mineralization		1	0.10	0		0		0		0	
Epithelium,hyperplasia		0		10	2.20	10	2.80	10	3.20	10	2.60
Hemorrhage		1	0.20	0		0		0		0	
Inflammation,granulomatous		0		10	2.20	10	2.50	10	2.60	10	2.80
Inflammation,perivascular		9	1.10	6	0.80	5	0.70	7	1.30	4	0.50
Lymphoid tissue,granuloma		0		10	2.20	10	2.70	10	2.30	10	2.70
Lymphoid tissue,hyperplasia		0		10	2.50	10	2.70	10	2.40	10	3.10
Pigment		0		10	3.00	10	3.00	10	3.30	10	3.80
HEART	# Ex	10		10		10		10		10	
Cardiomyopathy		5	0.50	7	0.80	8	0.80	5	0.50	10	1.00

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Severity Summary Table

PROJECT ID. NO: L62343R
DAYS: 131
FATES: SCHEDULED SACRIFICE
SEX: MALE

GROUP:		I-R		II-R		III-R		IV-R		V-R	
NUMBER OF ANIMALS:		10		10		10		10		10	
		#	SEV	#	SEV	#	SEV	#	SEV	#	SEV
URINARY BLADDER	# Ex	10		10		10		10		10	
Transitional epith,cell infilt		0		1	0.10	0		0		1	0.10
Calculus,micro observation		0		0		0		0		1	0.10
Mineralization		0		0		0		1	0.10	0	
STOMACH	# Ex	10		10		10		10		10	
LIVER	# Ex	10		10		10		10		10	
Cellular infiltrate,periportal		0		2	0.20	1	0.10	3	0.30	2	0.20
Hepatocyte,necrosis		1	0.10	5	0.50	6	0.70	3	0.30	7	0.70
Hepatocyte,vacuol,cyto		0		0		0		0		1	0.10
Hepatodiaphragmatic nodule		0		0		0		0		1	0.20
SPLEEN	# Ex	10		10		10		10		10	
SKIN	# Ex	10		10		10		10		10	
KIDNEY	# Ex	10		10		10		10		10	
Cortex,cellular infiltrate		0		1	0.10	0		1	0.10	0	
Hyaline droplets		10	1.30	10	1.40	10	1.30	10	1.00	10	1.00
Renal tubule,casts,protein		2	0.20	0		0		0		0	
Renal tubule,regeneration		4	0.40	0		2	0.20	3	0.30	0	
ADRENALS	# Ex	10		10		10		10		10	
THYMUS	# Ex	10		10		10		10		10	
BRAIN	# Ex	10		10		10		10		10	
STERNUM	# Ex	9		10		10		10		10	

* Severity calculated by the number of tissues examined.

SECTION IV

TABULATED ANIMAL DATA

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: 1 SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	001	002	003	004	005	006	007	008	009	010
NOSE	N	N			N	N	N		N	
Nasolacrimal duct,cell infilt	-	-	-	-	-	-	-	-	-	2
Nasolacrimal duct,hemorrhage	-	-	1	1	-	-	-	1	-	1
LARYNX	U	N		N	U	N	N		N	
Glands,cellular infiltrate	-	-	-	-	-	-	-	-	-	1
Respiratory epith,cell infilt	-	-	1	-	-	-	-	1	-	-
TRACHEA	N	N		N	N	N	N	N	N	N
Epithelium,cellular infilt	-	-	1	-	-	-	-	-	-	-
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN	N	N	N	N	N	N	U	U	N	N
LUNG							N			
Hemorrhage	-	-	-	-	-	-	-	-	1	1
Inflammation,perivascular	2	1	2	1	2	1	-	2	2	2
HEART		N	N							
Cardiomyopathy	1	-	-	1	1	1	1	2	2	1
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: I SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	001	002	003	004	005	006	007	008	009	010
LIVER		N	N		N					N
Hepatocyte,necrosis	1	-	-	2	-	1	1	-	-	-
Hepatocyte,vacuol,cyto	-	-	-	-	-	-	-	2	-	-
Hepatodiaphragmatic nodule	-	-	-	-	-	-	-	2	1	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	U	N	N
KIDNEY										
Hyaline droplets	2	2	1	2	1	1	2	2	1	2
Renal tubule,casts,protein	-	1	-	-	-	-	1	-	-	-
Renal tubule,regeneration	-	1	-	-	-	-	-	-	1	-
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: I SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	001	002	003	004	005	006	007	008	009	010
OTHER TISSUES AND LESIONS:										
MESENTERY: LN, congestion	-	-	-	-	-	-	-	-	-	2
TISSUE NOS: Fat, necrosis	-	-	-	-	-	-	-	3	-	-

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: II SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	041	042	043	044	045	046	047	048	049	050
NOSE										
Hyperplasia,goblet cell	2	2	2	3	3	3	3	4	3	3
Nasolacrimal duct,cell infilt	-	-	-	-	-	-	-	-	-	3
Nasolacrimal duct hemorrhage	-	1	-	-	-	-	-	-	1	-
Nasolacrimal duct,hyperplasia	-	-	1	-	-	-	-	-	-	-
Septum,cellular infiltrate	-	-	-	1	-	-	-	-	-	-
Inflammation	-	-	-	-	-	-	-	-	-	2
Pigment	-	-	-	-	-	-	-	-	-	1
LARYNX		N	N	N	N	N	N		N	N
Respiratory epith,hyperplasia	1	-	-	-	-	-	-	1	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN						U				
Granuloma	2	3	2	4	2	-	3	2	2	2
Hyperplasia	3	2	3	4	3	-	4	4	3	2
Pigment	2	2	1	1	2	-	2	2	2	1
LUNG										
Epithelium,hyperplasia	3	3	3	3	3	2	3	3	2	2
Inflammation,granulomatous	2	2	2	2	2	2	2	3	2	2
Inflammation,perivascular	-	-	-	-	-	-	1	-	-	-
Lymphoid tissue,granuloma	2	-	2	3	1	3	3	3	3	1
Lymphoid tissue,hyperplasia	2	2	2	3	1	3	3	3	3	1
Pigment	3	2	2	3	3	2	3	4	2	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: II SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	041	042	043	044	045	046	047	048	049	050
HEART				N				N		
Cardiomyopathy	1	1	1	-	2	1	1	-	1	1
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER				N	N		N	N	N	N
Hepatocyte,necrosis	-	1	-	-	-	1	-	-	-	-
Hepatocyte,vacuol,cyto	1	-	-	-	-	-	-	-	-	-
Hepatodiaphragmatic nodule	-	-	1	-	-	-	-	-	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Hyaline droplets	3	2	2	1	2	2	2	2	3	3
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: II SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	041	042	043	044	045	046	047	048	049	050
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: II SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	041	042	043	044	045	046	047	048	049	050
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN: Granuloma	2	3	3	3	3	2	3	2	3	3
MEDIASTINAL LN: Hyperplasia	2	3	3	3	2	2	3	3	3	3
MEDIASTINAL LN: Pigment	2	2	2	2	1	2	2	2	1	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: III SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	081	082	083	084	085	086	087	088	089	090
NOSE										
Hyperplasia,goblet cell	3	3	2	2	3	2	3	3	2	2
Nasolacrimal duct,hemorrhage	-	-	-	-	-	-	-	-	-	1
LARYNX	N	N	N	N		N	N	N	N	N
Respiratory epith,cell infilt	-	-	-	-	2	-	-	-	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN										
Granuloma	2	2	2	3	2	2	2	2	2	2
Hyperplasia	3	3	4	3	3	3	2	2	3	2
Pigment	1	1	1	1	1	1	1	1	1	1
LUNG										
Epithelium,hyperplasia	3	2	2	3	2	2	2	3	3	3
Inflammation,granulomatous	2	2	1	2	1	3	3	3	2	3
Inflammation,perivascular	-	2	2	1	-	2	2	2	1	1
Lymphoid tissue,granuloma	2	2	2	2	1	3	1	2	2	2
Lymphoid tissue,hyperplasia	2	2	1	2	1	3	3	2	2	3
Pigment	3	3	2	3	3	3	3	3	3	3
HEART	N	N	N		N			N	N	
Cardiomyopathy	-	-	-	1	-	1	1	-	-	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: III SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	081	082	083	084	085	086	087	088	089	090
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER	N		N	N			N	N	N	N
Cellular infiltrate,periportal	-	-	-	-	-	1	-	-	-	-
Hepatocyte,necrosis	-	1	-	-	1	-	-	-	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Cortex,cellular infiltrate	-	-	-	-	1	-	1	-	1	-
Hyaline droplets	1	2	2	2	2	2	2	2	2	3
Renal tubule,regeneration	-	-	-	-	-	-	-	-	1	-
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: III SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	081	082	083	084	085	086	087	088	089	090
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN: Granuloma	3	3	2	4	2	2	3	2	4	4
MEDIASTINAL LN: Hyperplasia	3	3	3	4	3	2	3	3	4	4
MEDIASTINAL LN: Pigment	1	1	1	1	2	2	2	2	1	1

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: IV SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	121	122	123	124	125	126	127	128	129	130
NOSE										
Hyperplasia,goblet cell	3	3	3	3	3	3	3	3	3	3
LARYNX	N	N	N	N	N	N	N	N	N	N
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN							U			
Granuloma	2	2	2	1	3	2	-	3	3	1
Hyperplasia	3	3	3	3	3	3	-	3	2	2
Pigment	2	2	2	2	1	1	-	3	2	1
LUNG										
Epithelium,hyperplasia	3	3	3	4	4	2	3	4	3	3
Inflammation,granulomatous	3	3	3	3	4	2	3	3	3	3
Inflammation,perivascular	1	2	2	-	1	1	1	-	-	-
Lymphoid tissue,granuloma	3	2	3	1	2	-	1	2	3	3
Lymphoid tissue,hyperplasia	3	2	3	1	2	-	2	2	3	3
Pigment	4	4	4	4	4	3	3	3	3	3
HEART	N				N			N		
Cardiomyopathy	-	1	1	1	-	1	1	-	1	1
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: IV SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	121	122	123	124	125	126	127	128	129	130
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER		N	N	N	N	N		N		N
Hepatocyte,necrosis	1	-	-	-	-	-	-	-	-	-
Hepatocyte,vacuol,cyto	-	-	-	-	-	-	1	-	2	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Cortex,cellular infiltrate	1	-	-	-	-	-	-	-	-	2
Hyaline droplets	3	2	2	2	2	2	3	2	3	3
Renal tubule,regeneration	1	1	-	-	-	1	-	-	-	-
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: IV SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	121	122	123	124	125	126	127	128	129	130
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN: Granuloma	2	2	3	2	3	2	1	2	3	4
MEDIASTINAL LN: Hyperplasia	3	3	3	4	3	4	3	3	3	3
MEDIASTINAL LN: Pigment	2	1	2	2	2	2	2	2	2	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: V SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	161	162	163	164	165	166	167	168	169	170
NOSE										
Hyperplasia,goblet cell	3	3	3	3	3	3	3	3	1	-
Nasolacrimal duct,hemorrhage	-	-	1	-	-	-	-	-	1	-
Nasolacrimal duct,hyperplasia	-	-	-	1	-	-	-	-	-	-
Epithelium,hyperplasia	-	-	-	-	-	-	-	-	-	2
LARYNX		N	N	N	N	N	N	N	N	
Lumen,mucus	3	-	-	-	-	-	-	-	-	-
Respiratory epith,hyperplasia	-	-	-	-	-	-	-	-	-	1
TRACHEA	N	N	N		N			N	N	N
Epithelium,hyperplasia	-	-	-	1	-	1	1	-	-	-
Epithelium,pigment	-	-	-	1	-	-	1	-	-	-
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN										
Granuloma	3	3	2	4	4	2	3	3	4	3
Hyperplasia	4	3	3	4	4	3	4	4	3	4
Pigment	2	2	2	2	2	3	3	2	2	1
LUNG										
Epithelium,hyperplasia	4	2	3	4	3	4	4	4	2	3
Inflammation,granulomatous	4	3	2	3	2	3	3	3	4	4
Inflammation,perivascular	-	1	-	-	-	-	-	-	-	-
Lymphoid tissue,granuloma	-	3	2	3	3	1	3	2	-	-
Lymphoid tissue,hyperplasia	4	4	2	3	3	3	2	4	-	-
Pigment	4	4	4	4	4	4	4	4	4	4

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: V SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	161	162	163	164	165	166	167	168	169	170
HEART						N	N	N	N	
Cardiomyopathy	1	1	1	1	1	-	-	-	-	1
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
STOMACH	N		N	N	N	N	N	N	N	N
Forestomach,epith,hyperplasia	-	1	-	-	-	-	-	-	-	-
LIVER		N			N			N		
Cellular infiltrate,periportal	1	-	-	-	-	-	-	-	-	-
Hepatocyte,necrosis	1	-	1	1	-	-	1	-	-	-
Hepatocyte,vacuol,cyto	-	-	-	-	-	1	-	-	-	1
Hepatodiaphragmatic nodule	-	-	-	-	-	-	-	-	1	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Hyaline droplets	3	3	3	2	2	2	2	3	2	2
Renal tubule,casts,protein	-	-	1	-	-	-	-	-	-	-
Renal tubule,mineralization	-	1	-	-	-	-	-	-	-	-
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: V SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	161	162	163	164	165	166	167	168	169	170
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L062343 GROUP: V SEX: MALE
DAYS: 89 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	161	162	163	164	165	166	167	168	169	170
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN: Granuloma	4	3	1	4	3	3	1	4	4	2
MEDIASTINAL LN: Hyperplasia	3	3	4	3	2	4	3	4	4	4
MEDIASTINAL LN: Pigment	2	2	3	2	1	3	3	2	1	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: I-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	021	022	023	024	025	026	027	028	029	030
NOSE		N	N		N	N	N	N		
Nasolacrimal duct,hemorrhage	1	-	-	1	-	-	-	-	1	1
LARYNX	N	N		N	N	N		N	N	N
Respiratory epith,cell infilt	-	-	1	-	-	-	1	-	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN		U	U	U	U	N	N	U	N	N
Pigment,refractile	1	-	-	-	-	-	-	-	-	-
LUNG								N		
Alveolus,mineralization	-	-	-	-	1	-	-	-	-	-
Hemorrhage	-	2	-	-	-	-	-	-	-	-
Inflammation,perivascular	1	1	2	1	1	2	1	-	1	1
HEART				N	N		N	N		N
Cardiomyopathy	1	1	1	-	-	1	-	-	1	-
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: I-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	021	022	023	024	025	026	027	028	029	030
LIVER	N	N	N	N	N	N		N	N	N
Hepatocyte,necrosis	-	-	-	-	-	-	1	-	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Hyaline droplets	2	1	1	1	1	1	1	2	2	1
Renal tubule,casts,protein	-	1	-	-	-	-	-	-	-	1
Renal tubule,regeneration	-	-	1	-	-	-	1	1	-	1
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	U	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: I-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	021	022	023	024	025	026	027	028	029	030
OTHER TISSUES AND LESIONS:										

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: II-R SEX: MALE
S: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	061	062	063	064	065	066	067	068	069	070
NOSE					N					
Hyperplasia,goblet cell	1	2	2	1	-	1	2	1	1	1
Nasolacrimal duct,hyperplasia	-	-	1	-	-	-	-	-	-	-
LARYNX		N		N	N	N	N		N	N
Respiratory epith,cell infilt	1	-	1	-	-	-	-	1	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN		U		U						
Granuloma	2	-	3	-	3	2	3	2	2	2
Hyperplasia	2	-	3	-	3	3	4	3	2	3
Pigment	2	-	2	-	2	2	2	2	2	2
LUNG										
Epithelium,hyperplasia	3	2	2	2	2	2	3	2	2	2
Inflammation,granulomatous	3	2	2	2	2	2	3	2	2	2
Inflammation,perivascular	1	2	-	1	2	1	-	-	1	-
Lymphoid tissue,granuloma	3	2	2	2	3	2	1	2	3	2
Lymphoid tissue,hyperplasia	3	2	3	2	3	2	3	2	3	2
Pigment	3	3	3	3	3	3	3	3	3	3
HEART		N				N				N
Cardiomyopathy	1	-	1	1	1	-	2	1	1	-

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: II-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	061	062	063	064	065	066	067	068	069	070
URINARY BLADDER	N	N		N	N	N	N	N	N	N
Transitional epith,cell infilt	-	-	1	-	-	-	-	-	-	-
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER						N	N		N	N
Cellular infiltrate,periportal	-	1	-	-	1	-	-	-	-	-
Hepatocyte,necrosis	1	-	1	1	1	-	-	1	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Cortex,cellular infiltrate	-	1	-	-	-	-	-	-	-	-
Hyaline droplets	1	2	2	1	1	2	1	1	1	2
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: II-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	061	062	063	064	065	066	067	068	069	070
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN - Granuloma	3	3	3	2	3	3	3	3	2	2
MEDIASTINAL LN - Hyperplasia	3	4	2	3	4	2	3	4	2	2
MEDIASTINAL LN - Pigment	3	2	3	2	2	3	3	2	2	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: III-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	101	102	103	104	105	106	107	108	109	110
NOSE									N	N
Hyperplasia,goblet cell	1	1	2	2	1	1	1	1	-	-
Nasolacrimal duct,hemorrhage	-	-	1	-	-	-	-	-	-	-
Hemorrhage	-	-	-	2	-	-	-	-	-	-
LARYNX	N		N	N	N	N	N	N	N	N
Respiratory epith,cell infilt	-	2	-	-	-	-	-	-	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN										
Granuloma	2	3	3	3	3	3	3	2	2	1
Hyperplasia	3	4	4	4	2	4	4	4	3	2
Pigment	2	2	2	2	2	2	2	2	2	1
LUNG										
Epithelium,hyperplasia	2	3	3	3	3	2	3	3	3	3
Inflammation,granulomatous	2	2	2	3	2	2	3	3	3	3
Inflammation,perivascular	-	-	1	2	-	1	2	-	1	-
Lymphoid tissue,granuloma	3	3	2	3	3	2	3	3	3	2
Lymphoid tissue,hyperplasia	3	3	2	3	3	2	3	3	3	2
Pigment	3	3	3	3	3	2	3	4	3	3
HEART								N	N	
Cardiomyopathy	1	1	1	1	1	1	1	-	-	1

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: III-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	101	102	103	104	105	106	107	108	109	110
URINARY BLADDER	N	N	N	N	N	N	N	N	N	N
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER				N			N	N	N	
Cellular infiltrate,periportal	-	-	-	-	-	-	-	-	-	1
Hepatocyte,necrosis	1	1	1	-	1	1	-	-	-	2
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Hyaline droplets	1	2	1	2	1	1	1	1	2	1
Renal tubule,regeneration	-	-	-	-	-	1	1	-	-	-
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: III-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	101	102	103	104	105	106	107	108	109	110
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN - Granuloma	3	2	2	3	3	2	3	2	2	2
MEDIASTINAL LN - Hyperplasia	3	3	2	3	3	2	4	2	3	3
MEDIASTINAL LN - Pigment	3	2	2	2	2	2	2	2	2	2
EYE - Cataract	-	-	-	-	-	-	2	-	-	-

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: IV-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	141	142	143	144	145	146	147	148	149	150
NOSE										
Hyperplasia,goblet cell	1	1	1	1	1	1	1	1	1	1
Nasolacrimal duct,hemorrhage	-	-	-	1	1	-	1	-	1	-
Nasolacrimal duct,hyperplasia	-	-	-	-	-	-	-	1	-	-
LARYNX	N	N	N	N	N	N	N	N		N
Respiratory epith,hyperplasia	-	-	-	-	-	-	-	-	1	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN										
Granuloma	3	2	2	3	3	2	3	3	3	2
Hyperplasia	2	3	3	3	3	2	3	3	3	3
Pigment	3	2	2	2	2	2	2	2	2	2
LUNG										
Epithelium,hyperplasia	2	3	3	4	4	4	3	3	3	3
Inflammation,granulomatous	2	2	3	3	3	3	2	2	3	3
Inflammation,perivascular	-	2	2	1	2	2	-	-	2	2
Lymphoid tissue,granuloma	2	2	3	2	3	3	2	2	2	2
Lymphoid tissue,hyperplasia	2	3	3	2	3	3	2	2	2	2
Pigment	3	3	3	4	4	4	3	3	3	3
HEART				N	N	N	N		N	
Cardiomyopathy	1	1	1	-	-	-	-	1	-	1

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: IV-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	141	142	143	144	145	146	147	148	149	150
URINARY BLADDER	N	N		N	N	N	N	N	N	N
Mineralization	-	-	1	-	-	-	-	-	-	-
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER	N	N	N					N		N
Cellular infiltrate,periportal	-	-	-	1	-	1	1	-	-	-
Hepatocyte,necrosis	-	-	-	1	1	-	-	-	1	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Cortex,cellular infiltrate	-	-	-	-	-	-	1	-	-	-
Hyaline droplets	1	1	1	1	1	1	1	1	1	1
Renal tubule,regeneration	-	1	-	-	-	-	1	-	-	1
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: IV-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	141	142	143	144	145	146	147	148	149	150
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN - Granuloma	3	3	3	2	3	3	2	3	3	2
MEDIASTINAL LN - Hyperplasia	4	3	3	2	2	3	2	4	3	3
MEDIASTINAL LN - Pigment	3	3	3	2	3	3	2	3	3	2

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: V-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	181	182	183	184	185	186	187	188	189	190
NOSE										
Hyperplasia,goblet cell	1	1	1	1	1	1	2	2	1	1
LARYNX	N	N		N	N	N	N	N	N	N
Respiratory epith,cell infilt	-	-	1	-	-	-	-	-	-	-
TRACHEA	N	N	N	N	N	N	N	N	N	N
ESOPHAGUS	N	N	N	N	N	N	N	N	N	N
PULMONARY LN										
Granuloma	4	2	4	3	3	4	3	3	3	3
Hyperplasia	2	2	4	3	4	4	3	4	4	4
Pigment	2	2	2	3	3	2	2	2	3	3
LUNG										
Epithelium,hyperplasia	3	3	3	2	2	3	3	2	2	3
Inflammation,granulomatous	2	3	3	3	2	3	3	3	3	3
Inflammation,perivascular	1	-	-	2	-	1	-	1	-	-
Lymphoid tissue,granuloma	2	2	3	4	3	2	2	3	3	2
Lymphoid tissue,hyperplasia	2	2	4	4	4	3	3	4	3	2
Pigment	4	4	4	3	3	4	4	4	4	4
HEART										
Cardiomyopathy	1	1	1	1	1	1	1	1	1	1

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: V-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	181	182	183	184	185	186	187	188	189	190
URINARY BLADDER	N	N	N		N	N		N	N	N
Transitional epith,cell infilt	-	-	-	1	-	-	-	-	-	-
Calculus,micro observation	-	-	-	-	-	-	1	-	-	-
STOMACH	N	N	N	N	N	N	N	N	N	N
LIVER								N	N	
Cellular infiltrate,periportal	1	-	1	-	-	-	-	-	-	-
Hepatocyte,necrosis	-	1	1	1	1	1	1	-	-	1
Hepatocyte,vacuol,cyto	-	1	-	-	-	-	-	-	-	-
Hepatodiaphragmatic nodule	-	-	-	-	2	-	-	-	-	-
SPLEEN	N	N	N	N	N	N	N	N	N	N
SKIN	N	N	N	N	N	N	N	N	N	N
KIDNEY										
Hyaline droplets	1	1	1	1	1	1	1	1	1	1
ADRENALS	N	N	N	N	N	N	N	N	N	N
THYMUS	N	N	N	N	N	N	N	N	N	N
BRAIN	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: V-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	181	182	183	184	185	186	187	188	189	190
STERNUM	N	N	N	N	N	N	N	N	N	N

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Tabulated Animal Data

PROJECT ID: L62343R GROUP: V-R SEX: MALE
DAYS: 131 FATES: SCHEDULED SACRIFICE

ANIMAL ID:	181	182	183	184	185	186	187	188	189	190
OTHER TISSUES AND LESIONS:										
MEDIASTINAL LN - Granuloma	4	4	4	4	4	4	4	3	2	2
MEDIASTINAL LN - Hyperplasia	3	4	3	3	3	2	2	2	2	2
MEDIASTINAL LN - Pigment	3	4	3	3	3	2	2	2	2	2

SECTION V

CORRELATION OF GROSS AND MICROSCOPIC (MICRO) FINDINGS

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: I SEX: MALE DAYS: 89

ANIMAL ID: 001 PATHOLOGY ID. NO: 915222-001 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 002 PATHOLOGY ID. NO: 915222-002 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 003 PATHOLOGY ID. NO: 915222-003 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 004 PATHOLOGY ID. NO: 915222-004 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: I SEX: MALE DAYS: 89

ANIMAL ID: 005 PATHOLOGY ID. NO: 915222-005 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 006 PATHOLOGY ID. NO: 915222-006 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 007 PATHOLOGY ID. NO: 915222-007 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 008 PATHOLOGY ID. NO: 915222-008 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

>TISSUE NOS, ABDOMINAL - MASS, 5X5X2 MM, TAN — TISSUE NOS- Fat, necrosis

>LIVER, MEDIAN LOBE - NODULE, RED — LIVER- Hepatodiaphragmatic nodule

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PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: I SEX: MALE DAYS: 89

ANIMAL ID: 009 PATHOLOGY ID. NO: 915222-009 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LIVER, MEDIAN LOBE - NODULE, 4X2X1 MM	LIVER- Hepatodiaphragmatic nodule

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ANIMAL ID: 010 PATHOLOGY ID. NO: 915222-010 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>MESENTERY - NODULE, RED	MESENTERY- LN, congestion

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: II SEX: MALE DAYS: 89

ANIMAL ID: 041 PATHOLOGY ID. NO: 915222-041 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>KIDNEYS, BILATERAL - MOTTLED	KIDNEY- Hyaline droplets
>LYMPH NODE, MEDIASTINAL - ENLARGED, 4X4X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 3X3X2 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment

ANIMAL ID: 042 PATHOLOGY ID. NO: 915222-042 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: II SEX: MALE DAYS: 89

ANIMAL ID: 043 PATHOLOGY ID. NO: 915222-043 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LIVER, MEDIAN LOBE - NODULE, 6X3X3 MM	LIVER- Hepatodiaphragmatic nodule
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 044 PATHOLOGY ID. NO: 915222-044 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 6X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: II SEX: MALE DAYS: 89

ANIMAL ID: 045 PATHOLOGY ID. NO: 915222-045 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X6X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNGS - LESION, MOTTLED	LUNG- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment

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ANIMAL ID: 046 PATHOLOGY ID. NO: 915222-046 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	No section taken
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: II SEX: MALE DAYS: 89

ANIMAL ID: 047 PATHOLOGY ID. NO: 915222-047 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNGS - LESION, MOTTLED, BLACK	LUNG- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 10X6X5 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment

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ANIMAL ID: 048 PATHOLOGY ID. NO: 915222-048 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, LEFT - ENLARGED, 5X5 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, 5X5 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment

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PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: II SEX: MALE DAYS: 89

ANIMAL ID: 049 PATHOLOGY ID. NO: 915222-049 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 050 PATHOLOGY ID. NO: 915222-050 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: III SEX: MALE DAYS: 89

ANIMAL ID: 081 PATHOLOGY ID. NO: 915222-081 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 082 PATHOLOGY ID. NO: 915222-082 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: III SEX: MALE DAYS: 89

ANIMAL ID: 083 PATHOLOGY ID. NO: 915222-083 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X5X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 084 PATHOLOGY ID. NO: 915222-084 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: III SEX: MALE DAYS: 89

ANIMAL ID: 085 PATHOLOGY ID. NO: 915222-085 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 086 PATHOLOGY ID. NO: 915222-086 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: III SEX: MALE DAYS: 89

ANIMAL ID: 087 PATHOLOGY ID. NO: 915222-087 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 6X5X5 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 088 PATHOLOGY ID. NO: 915222-088 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: III SEX: MALE DAYS: 89

ANIMAL ID: 089 PATHOLOGY ID. NO: 915222-089 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 11X6X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X5X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 090 PATHOLOGY ID. NO: 915222-090 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 12X8X5 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNGS - LESION, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: IV SEX: MALE DAYS: 89

ANIMAL ID: 121 PATHOLOGY ID. NO: 915222-121 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 122 PATHOLOGY ID. NO: 915222-122 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 8X7X5 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 6X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: IV SEX: MALE DAYS: 89

ANIMAL ID: 123 PATHOLOGY ID. NO: 915222-123 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 124 PATHOLOGY ID. NO: 915222-124 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 4X3X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNGS - LESION, MOTTLED	LUNG- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: IV SEX: MALE DAYS: 89

ANIMAL ID: 125 PATHOLOGY ID. NO: 915222-125 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, UNILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 126 PATHOLOGY ID. NO: 915222-126 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: IV SEX: MALE DAYS: 89

ANIMAL ID: 127 PATHOLOGY ID. NO: 915222-127 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNG - LESION, MOTTLED, BLACK	LUNG- Pigment

ANIMAL ID: 128 PATHOLOGY ID. NO: 915222-128 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: IV SEX: MALE DAYS: 89

ANIMAL ID: 129 PATHOLOGY ID. NO: 915222-129 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LIVER, LEFT LATERAL LOBE - FOCUS, 1X1 MM, WHITE	LIVER- Hepatocyte,vacuol,cyto
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5 MM DIAMETER, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 130 PATHOLOGY ID. NO: 915222-130 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED, BLACK	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: V SEX: MALE DAYS: 89

ANIMAL ID: 161 PATHOLOGY ID. NO: 915222-161 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X5X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 162 PATHOLOGY ID. NO: 915222-162 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNGS - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: V SEX: MALE DAYS: 89

ANIMAL ID: 163 PATHOLOGY ID. NO: 915222-163 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 4X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNGS - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 164 PATHOLOGY ID. NO: 915222-164 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNGS - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: V SEX: MALE DAYS: 89

ANIMAL ID: 165 PATHOLOGY ID. NO: 915222-165 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, BRONCHIAL - ENLARGED, 11X6X5 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment
>LYMPH NODE, MEDIASTINAL - ENLARGED	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment

ANIMAL ID: 166 PATHOLOGY ID. NO: 915222-166 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X5X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: V SEX: MALE DAYS: 89

ANIMAL ID: 167 PATHOLOGY ID. NO: 915222-167 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 168 PATHOLOGY ID. NO: 915222-168 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LUNG - LESION, BLACK, MOTTLED	LUNG- Pigment
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L062343 GROUP: V SEX: MALE DAYS: 89

ANIMAL ID: 169 PATHOLOGY ID. NO: 915222-169 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LIVER, MEDIAN LOBE - NODULE, 4X3X1 MM, RED	LIVER- Hepatodiaphragmatic nodule
>LYMPH NODE, MEDIASTINAL - ENLARGED, 7X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG - LESION, MOTTLED	LUNG- Pigment

ANIMAL ID: 170 PATHOLOGY ID. NO: 915222-170 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:89

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNGS - LESION, MOTTLED, BLACK	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: I-R SEX: MALE DAYS: 131

ANIMAL ID: 021 PATHOLOGY ID. NO: 915222-021 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 022 PATHOLOGY ID. NO: 915222-022 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 023 PATHOLOGY ID. NO: 915222-023 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 024 PATHOLOGY ID. NO: 915222-024 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: I-R SEX: MALE DAYS: 131

ANIMAL ID: 025 PATHOLOGY ID. NO: 915222-025 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 026 PATHOLOGY ID. NO: 915222-026 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 027 PATHOLOGY ID. NO: 915222-027 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 028 PATHOLOGY ID. NO: 915222-028 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: I-R SEX: MALE DAYS: 131

ANIMAL ID: 029 PATHOLOGY ID. NO: 915222-029 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

ANIMAL ID: 030 PATHOLOGY ID. NO: 915222-030 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD: RELATED HISTOPATHOLOGY:

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: II-R SEX: MALE DAYS: 131

ANIMAL ID: 061 PATHOLOGY ID. NO: 915222-061 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X6X7 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 3X3X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

ANIMAL ID: 062 PATHOLOGY ID. NO: 915222-062 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	No section taken
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: II-R SEX: MALE DAYS: 131

ANIMAL ID: 063 PATHOLOGY ID. NO: 915222-063 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 064 PATHOLOGY ID. NO: 915222-064 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: II-R SEX: MALE DAYS: 131

ANIMAL ID: 065 PATHOLOGY ID. NO: 915222-065 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 8X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 6X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

ANIMAL ID: 066 PATHOLOGY ID. NO: 915222-066 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, MOTTLED, GRAY	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: II-R SEX: MALE DAYS: 131

ANIMAL ID: 067 PATHOLOGY ID. NO: 915222-067 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 068 PATHOLOGY ID. NO: 915222-068 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: II-R SEX: MALE DAYS: 131

ANIMAL ID: 069 PATHOLOGY ID. NO: 915222-069 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 070 PATHOLOGY ID. NO: 915222-070 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: III-R SEX: MALE DAYS: 131

ANIMAL ID: 101 PATHOLOGY ID. NO: 915222-101 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 102 PATHOLOGY ID. NO: 915222-102 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: III-R SEX: MALE DAYS: 131

ANIMAL ID: 103 PATHOLOGY ID. NO: 915222-103 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, MOTTLED, BLACK	LUNG- Pigment

ANIMAL ID: 104 PATHOLOGY ID. NO: 915222-104 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X4X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: III-R SEX: MALE DAYS: 131

ANIMAL ID: 105 PATHOLOGY ID. NO: 915222-105 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 106 PATHOLOGY ID. NO: 915222-106 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: III-R SEX: MALE DAYS: 131

ANIMAL ID: 107 PATHOLOGY ID. NO: 915222-107 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 7X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X5X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>EYE, RIGHT - LESION, DIFFUSE, WHITE	EYE- Cataract
>LUNG, BILATERAL - LESION, MOTTLED, BLACK	LUNG- Pigment

ANIMAL ID: 108 PATHOLOGY ID. NO: 915222-108 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: III-R SEX: MALE DAYS: 131

ANIMAL ID: 109 PATHOLOGY ID. NO: 915222-109 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X4X2 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GREY, MOTTLED	LUNG- Pigment

ANIMAL ID: 110 PATHOLOGY ID. NO: 915222-110 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: IV-R SEX: MALE DAYS: 131

ANIMAL ID: 141 PATHOLOGY ID. NO: 915222-141 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 142 PATHOLOGY ID. NO: 915222-142 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X4X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 7X5X2 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: IV-R SEX: MALE DAYS: 131

ANIMAL ID: 143 PATHOLOGY ID. NO: 915222-143 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 144 PATHOLOGY ID. NO: 915222-144 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X4X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: IV-R SEX: MALE DAYS: 131

ANIMAL ID: 145 PATHOLOGY ID. NO: 915222-145 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X5X4 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 5X4X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 146 PATHOLOGY ID. NO: 915222-146 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: IV-R SEX: MALE DAYS: 131

ANIMAL ID: 147 PATHOLOGY ID. NO: 915222-147 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 148 PATHOLOGY ID. NO: 915222-148 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, MOTTLED, BLACK	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: IV-R SEX: MALE DAYS: 131

ANIMAL ID: 149 PATHOLOGY ID. NO: 915222-149 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X4X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 8X7X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 150 PATHOLOGY ID. NO: 915222-150 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: V-R SEX: MALE DAYS: 131

ANIMAL ID: 181 PATHOLOGY ID. NO: 915222-181 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

ANIMAL ID: 182 PATHOLOGY ID. NO: 915222-182 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: V-R SEX: MALE DAYS: 131

ANIMAL ID: 183 PATHOLOGY ID. NO: 915222-183 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 10X5X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 6X4X3 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 184 PATHOLOGY ID. NO: 915222-184 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 8X6X3 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: V-R SEX: MALE DAYS: 131

ANIMAL ID: 185 PATHOLOGY ID. NO: 915222-185 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LIVER, MEDIAN LOBE - MASS, 16X10X12 MM	LIVER- Hepatodiaphragmatic nodule
>LYMPH NODE, MEDIASTINAL - ENLARGED, 6X4X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 7X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, GRAY, MOTTLED	LUNG- Pigment

ANIMAL ID: 186 PATHOLOGY ID. NO: 915222-186 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL
MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N
MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: V-R SEX: MALE DAYS: 131

ANIMAL ID: 187 PATHOLOGY ID. NO: 915222-187 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 188 PATHOLOGY ID. NO: 915222-188 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, 5X4X2 MM, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, 6X5X4 MM, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

PATHOLOGY ASSOCIATES, INC.
THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS
IITRI PROJECT NUMBER L06234, STUDY NUMBER 3

Correlation of Gross & Micro Findings

PROJECT ID: L62343R GROUP: V-R SEX: MALE DAYS: 131

ANIMAL ID: 189 PATHOLOGY ID. NO: 915222-189 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

ANIMAL ID: 190 PATHOLOGY ID. NO: 915222-190 PATHOLOGIST: MT
ANIMAL FATE: SCHEDULED SACRIFICE
DAYS ON TEST:131

REFERENCE TO NECROPSY RECORD:	RELATED HISTOPATHOLOGY:
>LYMPH NODE, MEDIASTINAL, BILATERAL - ENLARGED, BLACK	MEDIASTINAL LN- Hyperplasia, MEDIASTINAL LN- Pigment
>LYMPH NODE, BRONCHIAL, BILATERAL - ENLARGED, BLACK	PULMONARY LN- Hyperplasia, PULMONARY LN- Pigment
>LUNG, BILATERAL - LESION, BLACK, MOTTLED	LUNG- Pigment

SECTION VI

QUALITY ASSURANCE STATEMENT

QUALITY ASSURANCE STATEMENT

This histopathology project was inspected and audited by the PAI Quality Assurance Unit (QAU) as required by the Good Laboratory Practice (GLP) standards promulgated by the U.S. Environmental Protection Agency. Results of these activities indicate that the portions of the study performed by PAI conformed with GLP standards and applicable Standard Operating Procedures. The pathology narrative report is an accurate reflection of the recorded data. The following table is a record of the inspections/audits performed and reported by the QAU:

Date of Inspection	Phase Inspected	Date Findings Reported to Management and Study Pathologist
**19-Feb-92	Tissue Trimming	20-Feb-92
*09-Dec-91	Processing/Embedding	10-Dec-91
*02-Jan-92	Microtomy	03-Jan-92
**28-Jan-92	Staining	29-Jan-92
**28-Jan-92	Coverslipping	29-Jan-92
*17-Jan-92	Labeling	17-Jan-92
*12-Dec-91	Quality Control/Checkout	12-Dec-91
**12-May-92	Individual Animal Data	27-May-92
**12-May-92	Data Entry	27-May-92
**15-May-92	Computer Validation	27-May-92
**27-May-92	Draft Pathology Report	27-May-92
**18-Dec-92	Final Pathology Report	18-Dec-92

*General quarterly phase inspection
**Inspection specific for Study Number

In accordance with the PAI Quality Assurance Division's Standard Operating Procedures, all critical phase inspections are conducted on a random basis quarterly or more frequently. Those general phase inspections listed are the most recent conducted during the period each task associated with this project was performed.

Quality Assurance Unit
PAI Illinois Division

18-Dec-92
Date

Thirteen-Week Inhalation Toxicity Study with Aerosol Mixtures of Fog Oil and Graphite Particles in F344/N Male Rats, Project Number L06234, Study Number 3

PART ONE

APPENDIX C

STUDY PROTOCOL

Inhalation Toxicity of Single Materials
and Mixtures, Phase IV.
Contract No. DAMD17-89-C-9043
IITRI Project No. L06234, Study No. 3

PROTOCOL

I. Study Title: **THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS**

II. Sponsor and Sponsor's Representative:

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
JACK DACRE, PH.D., CONTRACTING OFFICER'S TECHNICAL REPRESENTATIVE (COTR)
FORT DETRICK
FREDERICK, MARYLAND 21702-5012

III. Testing Laboratory:

IIT RESEARCH INSTITUTE (IITRI)
LIFE SCIENCES RESEARCH DEPARTMENT
10 WEST 35th STREET
CHICAGO, ILLINOIS 60616

IV. Protocol Approval:

1. Study Director: Jeannie Bradof (Jeannie Bradof) Date: 9/20/91
2. Study Toxicologist: John Drummond (Dr. John Drummond) Date: 9-20-91
3. Prin. Invest./ Manager, Inhalation Tox.: Catherine Aranyi (Catherine Aranyi) Date: 9-20-91
4. Manager, Quality Assurance: Ronald Boyne (Ronald Boyne) Date: 9-20-91
5. Sponsor (COTR): Jack B. Dacre (Dr. Jack Dacre) Date: 10-1-91

V. Objective:

This study is conducted to determine if a thirteen-week inhalation exposure of rats to mixtures of aerosols of a petroleum-based liquid (fog oil) and a solid particulate (graphite) will result in synergistic, antagonistic, or additive effects in selected biologic end points.

As in the Phase III study (SN 2), a single daily duration (4 hr/day) and weekly frequency (4 exposures per week) will be used for the thirteen-week exposure study which will be conducted with male F344/N rats. Biologic end points will include pulmonary lavage parameters, selected pulmonary function parameters, lung weights, histopathology, and clinical pathology. These end points will be evaluated in animals sacrificed within 24 hrs after the last exposure and after a six-week recovery period. All animals on test will be monitored for in-life clinical signs, body weights, and selected groups for food consumption.

VI. Route of Exposure and Rationale:

Whole body inhalation exposure was selected in order to most closely approximate the exposure route of military personnel to airborne materials under field conditions.

VII. Proposed Schedule of Events:

EVENT	DATE(S)
Animal Receipt:	week of 09/23/91
Quarantine Period:	receipt (week of 09/23/91) - 10/06/91
Quarantine Necropsy and Pre-exposure Health Examination:	10/04/91
Randomization and Identification:	10/03-04/91
First Day of Exposures:	10/07/91
Body Weights and Clinical Observations:	10/7,11,18,25/91 11/1,8,15,22,29/91 12/6,13,20,27/91 01/3,10,17,24,31/92 02/7,14/92
Mortality/Moribundity Observations:	Daily 10/07/91-02/15/92
Non-exposure Holidays:	11/28/91, 12/25/91, 01/01/92

Last Day of Exposures[a]: 01/03/92

Post-Exposure Assays
(preceded by final body
weights):

Pulmonary Lavage Parameters/ Pulmonary Function:	01/03-04/92
Pathology/Clin. Path.:	01/03/92

Post-Recovery Assays
(preceded by final body
weights):

Pulmonary Lavage Parameters/ Pulmonary Function:	02/14-15/92
Pathology/Clin. Path.:	02/14/92

VIII. Test Substances:

1. Identification:

   a. Type II Graphite

      Lot No. 7154B

   b. Fog Oil, a petroleum-based liquid [PBL]

      Shipping Code No. SGF-2, MIL-F-12070C & AM 2, 9150-00-261-7895

      Lot 12, DLA-400-87-C-1658

2. Receipt:

   The test substances were supplied by the Sponsor (U.S. Army, Biomedical Research and Development Laboratory, Fort Detrick, Frederick, MD) and shipped from Aberdeen Proving Ground, MD (PBL) and Chamberlain MRC, Hunt Valley, MD (graphite). A fiber board drum containing a total of 120 lb of the graphite powder was received on September 9, 1991. The fog oil was received in one 55 gallon steel drum on May 1, 1989.

3. Storage:

   Both test substances will be stored in the original shipping containers at ambient room temperature (approx. 22°C) in a secure area.

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[a] Exposure terminations are staggered: See Attachment A and Section XI for details.

4. Assay:

The sponsor is responsible for all chemical analyses pertaining to the characterization, stability and homogeneity of the bulk test substances and attendant documentation.

5. Handling and Hazards to Personnel:

Personnel will wear a laboratory smock, latex gloves, a respirator fitted with HEPA filter cartridges, and eye protection when working with the neat test substances, unless other information is provided by the Sponsor.

6. Disposition:

All quantities of test substances which are dispensed will be documented (SOP: LSM-012). At the time of the acceptance of the final report by the Sponsor, arrangements will be made for proper disposal or the return of residual test substances to the Sponsor; IITRI will not be required to retain any samples. A reserve sample will be sent to the Sponsor upon initiation of the study and retained by the Sponsor.

IX. Inhalation Exposure:

1. Inhalation Exposure Laboratories:

The supply air for the laboratories and inhalation exposure chambers is preconditioned and automatically controlled with a thermostat and humidistat to maintain the temperature and humidity ranges of 24±3°C and 50±20%RH. The single-pass conditioned room air is introduced into the chambers through individual inlet filter assemblies consisting of a coarse filter and a HEPA filter.

The exhaust from the individual aerosol exposure chambers passes through a bag-type large surface area pre-filter, followed by a HEPA filter and connected by flexible ducting to a common 20 cm diameter duct. The combined exhaust is moved by a pressure blower and exhausted outside the building. Each chamber airflow is individually controlled with a gate valve and monitored with a calibrated orifice meter located downstream of the filter. Exhaust filter loading is monitored by determining pressure drop across the filters with a magnahelic pressure differential gauge.

The inhalation chambers will be operated at an air flow rate of approximately 500 liters per minute and maintained at a pressure that is negative to the laboratory environment.

The chamber used for the control animals is located in a separate laboratory with an exhaust system which is independent of the experimental test chambers.

2. Daily Exposure Schedule and Chamber Assignment:

The study will be conducted in five 1-m^3 Rochester-type inhalation exposure chambers. The fog oil aerosol target concentrations will be 250, 500, and 1000 mg/m^3; the graphite aerosol target concentration will be 100 and 200 mg/m^3. Control animals will be exposed to filtered air. Exposures will be conducted for 4 hr/day and exposure frequencies will be four times per week. Exposures will not be conducted on holidays.

3. Test Atmosphere Generation:

The two aerosol generators employed in these studies were developed at Oak Ridge National Laboratories (ORNL). The two generation systems are interfaced in a "Y" section of the aerosol transport flexible ducting just prior to the chamber inlet mixing plenum. Each generation system (PBL and Graphite) is operated independently. Individual aerosol generation systems are used for each inhalation exposure chamber (SOP: MBIH-111).

3.1. The Liquid Aerosol Generator:

The liquid aerosol generator for the petroleum-based fog oil is a modification of a generator developed at ORNL for producing an aerosol from diesel fuel. The generator employs an evaporative/condensation technique and consists of an immersion heater mounted inside of a stainless steel tube. Temperature of the heater is automatically controlled. The test substance (PBL) is introduced at a controlled rate by a metering pump which determines aerosol concentration onto the immersion heater and transported to the chamber aerosol inlet by nitrogen carrier gas.

3.2 The Graphite Particulate Aerosol Generator:

The graphite aerosol generation system consists of a compressed air-driven jetmill dispersing unit fed by a screw feeder which controls the delivery rate of the test substance bulk material. The generator is interfaced to the chamber air supply through a glass tee which removes large particles. The fine particles are transported to the chamber aerosol inlet.

4. Test Atmosphere Monitoring:

4.1 Aerosol Mass Concentration:

The aerosol mass concentration in each chamber will be determined by collecting the aerosol on 45 mm diameter glass-fiber filters placed in a close face plastic filter holder and pre-weighed with an analytical balance. In addition, one filter-collected sample will be chosen at random for each day from each of the chambers containing

PBL/Graphite mixtures and analyzed chemically to determine the amount of PBL aerosol. The samples will be collected at a constant flow rate using a positive displacement diaphragm-type vacuum air pump. A dry gas meter connected to the positive pressure side of the pump will be used to record the corresponding total volume of chamber air sampled. Samples from individual chambers will be collected at a minimum of once per hour during each animal exposure period (MBIH-2R2).

At the outlet of the liquid and solid aerosol generators, back-scattering photosensors will be used for monitoring the generator operation. These sensors will be employed as real-time indicators of short term changes in aerosol concentration and used in guiding laboratory personnel in making necessary adjustments in generator settings if concentration excursions are encountered (SOP: MBIH-7R1).

4.2 Aerosol Particle Size:

Aerosol particle size distribution will be monitored in each of the chambers with a Quartz Crystal Microbalance (QCM)-based cascade impactor. Determination of aerosol particle size distribution will be conducted during the first week of the study (SOP: MBIH-8R1).

4.3 Oxygen Monitoring:

A commercial solid state oxygen analyzer will be used for monitoring percentage of oxygen in the chamber atmosphere. Oxygen concentration in each chamber will be determined in the first week of the animal exposures (SOP: MBIH-11).

4.4 Temperature and Humidity:

Temperature and percent relative humidity (RH) in the individual chambers and laboratories will be monitored manually and recorded at least once each hour during each exposure period with a portable hand-held thermohygrometer.

4.5 Chemical Analysis:

PBL/Graphite mixtures collected on glass fiber filters will be placed in screw-capped glass vials immediately after weighing for chemical analysis. The samples will be extracted with methylene chloride and sonication for 5 min. The samples will be filtered through a 0.45 u Teflon filter. The extracts will be analyzed (both qualitative and quantitative) by gas chromatography. The basis of the qualitative analysis will be a visual comparison of the chromatogram of the bulk PBL to aerosol-generated PBL/Graphite mixtures. Quantitation of PBL will be based on measured peak heights of the samples compared to standards prepared from the bulk PBL. One filter from each exposure chamber will be analyzed for each exposure day.

X. Animals:

1. Justification/Source:

The F344/N rat was chosen for this study since it is a well characterized, sensitive test strain with a considerable amount of toxicologic background data available. The animals will be obtained from Taconic Farms Inc., Germantown, NY. Two hundred male F344/N rats will be used for this study. The animals will be 4-5 weeks of age at arrival and will weigh approximately 55-85 grams.

2. Caging/Housing:

The inhalation studies will be conducted using 1-m^3 Rochester-type inhalation exposure chambers. The test animals will be housed in suspended stainless steel wire-mesh inhalation cages on mobile racks. Each mobile rack holds 24 cage units and each cage unit contains four individual cubicles for a total capacity of 96 animals per rack. Each cubicle measures 18.4 x 16.5 x 15.9 cm. The animals will be double-housed upon arrival to help them become acclimated to their new surroundings and to help them learn to use the automatic watering system. The animals will be housed individually at the time of making group assignments and will remain individually housed throughout the course of the study.

During the quarantine period and during non-exposure periods, the animals will be maintained in animal rooms located directly across the corridor from the exposure laboratories. These animal rooms and exposure laboratories are located on a semi-isolated corridor. Following randomization, the control group animals will be maintained in a separate animal room for the duration of the study. Each day just prior to the exposure periods, the animals will be transferred from the animal rooms to the exposure laboratories by removing the cage units from the mobile racks and placing them in the exposure chambers. The animals will be returned to their respective mobile racks and transferred back to the animal rooms following the exposure periods.

3. Animal Room Environmental Conditions:

The conditioned air supplied to the animal rooms and exposure laboratories is 100% fresh filtered air. Air flow in the animal rooms will provide at least 10 complete air changes per hour. The animal room conditioned air system is connected to an alarm system which is continuously monitored at the main security desk 24 hours a day. The system is designed to notify maintenance personnel of any malfunction in the operation of the air handling equipment.

The environmental conditions in the animal rooms will be monitored and recorded twice daily on weekdays and once/day

on the weekends. The ambient laboratory and animal room temperatures and relative humidities will be maintained at 24±3°C and 50±20%RH.

The lighting cycle in the animal rooms will be maintained on a 12 hour light/dark cycle.

4. Cleaning and Sanitation:

Prior to the animals' arrival at IITRI, the exposure laboratories, exposure chambers, mobile racks and cages, and the animal rooms will be cleaned and sanitized according to SOP: NTP-315R3, -317R1, and -322R4. The exposure chambers (MBIH-110), cage units, mobile racks, feeders, and excrement pans will be cleaned and sanitized at least weekly thereafter except during quarantine when cleaning will occur biweekly. The floors of the animal rooms and laboratories will be mopped on each exposure day during the course of the study and at least twice weekly during the quarantine and recovery periods.

The automatic watering system delivery lines are flushed automatically every eight hours for a period of 15 minutes per flush cycle to ensure a continuous supply of fresh potable drinking water. Water samples will be obtained prior to the animals' arrival and submitted for microbiological evaluation.

5. Cage Boards:

Deotized animal cage boards (Shepherd Specialty Papers, Inc., Kalamazoo, MI) will be placed in the excrement pans below the cage units to absorb liquid waste during non-exposure periods. The boards will be changed at least 3 times per week.

6. Food:

Food will be Purina Certified Rodent Chow No. 5002 which will be analyzed by the manufacturer for contaminants and nutrient levels. The diet will be available ad libitum during non-exposure hours only. Food analysis reports, provided by the manufacturer, will be maintained with the study records. The food will be stored on pallets in a well ventilated room and will be used for no more than 180 days post-milling. No known contaminants are expected to be present in the feed at levels known to be capable of interfering with the conduct of the study.

7. Water:

The mobile racks and animal rooms will be equipped with automatic watering systems. The drinking water supplied will be filtered City of Chicago drinking water. The water

will be available ad libitum during non-exposure periods only. The watering system will be checked daily to ensure proper functioning. Copies of the bimonthly results of the City of Chicago water analysis will be maintained with the study records and will be included in the final report. No known contaminants are expected to be present in the water at levels known to be capable of interfering with the conduct of the study.

8. Animal Receipt and Quarantine:

8.1 Receipt and Housing:

The exterior surfaces of the shipping containers will be examined for damage, and if accepted, wiped down with a dilute solution of sodium hypochlorite as the containers are introduced into the corridor of the inhalation facility. The animals will be taken directly from their shipping containers and housed in the wire mesh inhalation cages (SOP: LASS22R3).

8.2 Observation:

During this period, the animals will be observed cage-side at least daily for obvious signs of disease such as general unthriftiness, poor hair coat, discharges from body orifices, abnormal feces, etc. Notes of observations on any specific animals will be recorded in the comments section of the Mortality/Moribundity Data Sheet. Sixty animals will be weighed within 48 hr of receipt. Within three working days of receipt, the animals will be evaluated by a laboratory animal veterinarian. Following randomization, two animals will be selected from the excess stock for quarantine sacrifice. These animals will be bled for a standard rat virus profile (Microbiological Associates, Rockville, MD) followed by a gross necropsy. Lesions discovered during the necropsy may be evaluated by submitting appropriate samples for microbiological culture and identification and/or tissues for histological examination. The total time for the quarantine period will be defined as from receipt to the day prior to exposure initiation (see Section VII).

9. Identification:

All rats used in the study will be identified by tail tattoo representing a unique number within the population making up the study. The raw data records and specimens will also be identified by the unique test animal number.

The animal identification numbers and cage assignments for the study are shown in Attachment A.

10. Randomization:

Rats will be assigned to groups prior to exposure initiation using a stratified weight method whereby animals are ranked

in order, by weight, and assigned to study groups in random order (SOP: GT-315).

XI. Experimental Design:

The study will include five exposure groups: one material (fog oil) will be tested at three concentrations (250, 500, and 1000 mg/m^3), with the middle 500 mg/m^3 concentration being tested in combination with each of the two concentrations used for the graphite aerosols (100 and 200 mg/m^3), and the low and high fog oil concentrations being tested in combination with the low and high graphite aerosol concentrations, respectively. The fifth group will be a filtered air control. These combinations will be tested in five inhalation chambers as follows:

Group	Chamber No.	Concentration in mg/m^3 of Fog Oil	Graphite
I	6	0	0
II	5	250	100
III	3	500	100
IV	1	500	200
V	2	1000	200

Based on the results of the Phase III (SN2) study, groups consisting of 40 male F344/N rats will be exposed to the above-listed five conditions 4 hr/day, four days/week (Monday through Thursday) for thirteen weeks and a recovery period of six weeks will be used. Exposures will not be conducted on holidays. Biological end points will be determined in animals sacrificed within 24 hr after the last exposure (EXP) and after a six-week recovery period (REC). Exposures in the last exposure week will be shifted for some LAV/PF animals to accommodate the manpower limitation-caused need for two assay dates (See Attachment A for details).

The distribution of the 200 rats into the end point groups (PATH and LAV/PF) and assay times (EXP and REC) is shown in Table 1. Details of the exposure and assay dates for the different end points and the animal numbers to be assigned for each group are summarized in Attachment A.

XII. In-Life and Terminal Observations:

1. Toxicologic End Points (All animals):

1.1 Body Weights:

The body weights will be measured and recorded individually to the nearest whole gram. The body weights will be measured at study initiation, weekly during the thirteen-week exposure period and the subsequent six-week recovery period, and immediately before termination. The first

Table 1. Experimental Design[a]

Expo. Group Code[c]	Aerosol Conc., mg/m³ PBR	Aerosol Conc., mg/m³ Graphite	Total Number of Rats	In-Life Testing: Daily Obs[d]	In-Life Testing: Clinical Signs[e]	In-Life Testing: Body Wt.[f]	In-Life Testing: Food Consumpt.[g]	EXP (Post-Exposure) Assays[b]: LAV[h]	EXP (Post-Exposure) Assays[b]: PF[i]	EXP (Post-Exposure) Assays[b]: PATH[j]	REC (Post-Recovery) Assays[b]: LAV[h]	REC (Post-Recovery) Assays[b]: PF[i]	REC (Post-Recovery) Assays[b]: PATH[j]
I	0	0	40	40	40	40	10	10	(8)	10	10	(8)	10
II	250	100	40	40	40	40	10	10	(8)	10	10	(8)	10
III	500	100	40	40	40	40	10	10	(8)	10	10	(8)	10
IV	500	200	40	40	40	40	10	10	(8)	10	10	(8)	10
V	1000	200	40	40	40	40	10	10	(8)	10	10	(8)	10

a Numbers represent sample sizes.

b One (PATH) or two (LAV, PF) assay days occur at each timepoint (EXP = within 24 hr of the last exposure; REC = six weeks after the last exposure).

c Exposure Classes II - V receive aerosols of the test substance mixtures. Exposure Class I is filtered air control.

d Twice/day on weekdays (once/day on weekends) for mortality and moribundity.

e Weekly.

f Weekly for the thirteen-week exposure period and the subsequent six-week recovery period (where applicable) and immediately before termination.

g Weekly for selected animals.

h LAV = Pulmonary lavage assays (see text). These rats are shared with pulmonary function tests, which will test 8 of the available 10 rats.

i PF = Pulmonary function assays (see text). These rats are shared with pulmonary lavage tests.

j PATH = Histopathology/clinical pathology assays (see text).

weighing will be in the morning prior to the first exposure. Subsequent weighings will be on Fridays (a non-exposure day) in the morning. Body weight gains will be calculated as change relative to the body weight measurement taken prior to the first exposure.

1.2 Clinical Observations:

All animals will be observed twice daily on weekdays (once daily on the weekends and holidays) for moribundity and mortality (SOP: NTP-420R3). Each animal will be formally examined once each week at the time of body weight collection for clinical signs of pharmacologic and toxicologic effects of the exposure (SOP: GT-401R1). On exposure days the first mortality/ moribundity observation will coincide with food removal and chamber loading operations.

The study toxicologist, or veterinarian, will visit the laboratory at least once a week to confirm, correct or expand the clinical observations. Any animal whose condition suggests that it may not survive until the next observation based upon established criteria (SOP: NTP-409R4) will be euthanized and necropsied immediately, with the tissues retained in formalin. Gross lesions found at necropsy will be documented and the affected tissues processed for histopathological examination.

1.3 Food Consumption:

Average food consumption for each animal in the PATH "recovery" groups will be measured weekly during the thirteen exposure and six recovery weeks of the study. A measured amount of food will be offered to the rats at the time of body weight measurements. On the next scheduled day when another measured amount of food is offered, the remaining food from that previously offered will be removed and weighed. The food consumption will be calculated from the measured differences between the provided and recovered food quantities.

2. Pathology/Clinical Pathology (PATH):

2.1 Blood Collection and Clinical Pathology Examinations:

Blood samples will be collected and analyzed from the pre-designated PATH rats for the list of hematology and clinical chemistry assays shown in Table 2. Samples will be collected and analyzed on the same day. Samples will not be collected from any moribund animals in the pre-designated PATH evaluation groups. Blood collection and analysis will be conducted in a random order (SOP: NTP-414R3). Blood will be collected via the retroorbital sinus (SOP: NTP-419R1) under CO_2 anesthesia (SOP: NTP-413R3).

TABLE 2. LIST OF CLINICAL PATHOLOGY ASSAYS

Hematology Assays

Erythrocyte Count (SOP: CP 709)
Mean Corpuscular Volume (SOP: CP 709)
Mean Corpuscular Hemoglobin (Derived) (SOP: CP 709)
Mean Corpuscular Hemoglobin Concentration (Derived)
(SOP: CP 709)
Hemoglobin (SOP: CP 709)
Hematocrit (Derived) (SOP: CP 709)
Erythrocyte Morphologic Assessment (SOP: CP 745.1R1)
Leukocyte Count (SOP: CP 709)
Leukocyte Differential Count: (SOP: CP 745R1)
Reticulocyte Count (SOP: CP 760R3) - if anemia is present
Platelet Count and Morphologic Assessment
(SOP: CP 709 and SOP: CP 745.1R1)

Clinical Chemistry Assays

Total Protein (SOP: CP 644R4)
Albumin (SOP: CP 626R4)
Blood urea nitrogen (SOP: CP 629R4)
Creatinine (SOP: CP 633R4)
Alanine aminotransferase (SOP: CP 642R4)
Alkaline phosphatase (SOP: CP 627R4)
Creatine kinase (SOP: CP 624R4)
Total bile acids (SOP: CP 646R1)
Total cholesterol (SOP: CP 631R5)
Glucose (SOP: CP 634R4)
Sorbitol dehydrogenase (SOP: CP 647R2)
Calcium (SOP: CP 630R4)
Inorganic phosphate (SOP: CP 638R4)
Triglycerides (SOP: CP 643R4)

2.2 Necropsy:

All scheduled necropsies will be performed in the presence of and under the supervision of the IITRI-PAI pathologist. All unscheduled necropsies (moribund sacrifice and spontaneous deaths) will be supervised by the pathologist to the maximum extent possible, and will be performed as soon after death as possible. Animals for unscheduled necropsies will not be frozen, and every attempt will be made to refrigerate animals for no longer than eight hours prior to the necropsy. Animals will be euthanized with CO_2 according to SOP: NTP-421R1.

Scheduled and unscheduled necropsies, will follow the specific necropsy procedures, as described in SOP: PAI-IL-018. A complete necropsy is defined as external examination including body orifices and examination and fixation of all tissues specified for the study. Complete necropsies will be performed unless autolysis precludes all or part of the examination. In all cases, available tissues will be collected as outlined in subsequent sections of this protocol.

The following tissues will be collected and placed in fixative (tissues marked with an asterisk will be processed and examined histologically):

Salivary Gland (Mandibular)	Lymph Nodes (Submandibular)
Mammary Gland	Sternum *
Thymus *	Thyroid
Heart *	Parathyroid
Lung *	Esophagus *
Trachea *	Testes
Pulmonary Lymph Nodes *	Prostate
Liver *	Urinary Bladder *
Spleen *	Duodenum
Seminal Vesicles	Ileum
Stomach *	Colon
Adrenals *	Jejunum
Sciatic Nerve	Cecum
Brain *	Mesenteric Lymph Node
Eyes	Kidney *
Spinal Cord	Skeletal Muscle
Skin *	Pituitary
Gross Lesions *	Larynx *
Animal Identification	Nasal Turbinates*

All indicated tissues and/or organs will be examined in situ, then dissected from the carcass, re-examined, including cut surfaces, and fixed in 10% neutral buffered formalin. Tails, used for identification purposes, will be saved in formalin.

Rats designated for scheduled necropsy and histopathologic examination will be anesthetized with carbon dioxide and exsanguinated from the abdominal aorta, either within 24 hr

following the last exposure or after a six-week recovery period following the exposures. All scheduled necropsies will be initiated promptly after an animal is killed and will be performed on all PATH-designated animals.

2.3 Organ Weights:

Lung weights will be obtained at necropsy from all animals surviving until the end of the study (SOP: NTP-408R3). Lungs will be weighed to the nearest 1.0 mg. Organ weight/body weight ratios will be calculated.

2.4 Histology/Histopathology:

Each animal will be assigned a unique histology accession number. Tissue trimming, processing, embedding, sectioning and staining (hematoxylin and eosin) will be done in accordance with SOP's PAI-IL-005 through -011. The Individual Animal Necropsy Form for each animal will be available for the technician at the time of trimming. Once all aspects of histology are completed, the residual wet tissues, blocks and slides will be prepared for long-term archiving and/or shipped to the Sponsor. Slides will be prepared according to the embedding scheme shown below.

Embedding Scheme

Slide 1	Nasal turbinates (3 sections)
Slide 2	Larynx, trachea (cross and longitudinal), esophagus, and pulmonary lymph nodes
Slide 3	Lung (whole mount with all lobes presented to include the main bronchus)
Slide 4	Heart, stomach, urinary bladder
Slide 5	Liver (sections from two lobes), spleen, and skin
Slide 6	Kidneys (right and left), adrenals (right and left), and thymus
Slide 7	Brain
Slide 8	Sternum

All indicated tissues for all treatment groups, Post-Exposure and Recovery, will be examined microscopically. All microscopic observations will be entered into the IITRI/PAI automated pathology system (Labcat) for generation of individual animal summary tables.

3. Pulmonary Function (PF):

The pulmonary function parameters will be measured using an acrylic plethysmograph (BUXCO Electronics, Inc.) equipped to allow measurement of airflow and plethysmograph, airway and esophageal pressure for anesthetized animals.

Each test anim. (which will also be used later for the LAV measurements) will be weighed (tattoo I.D. also recorded), anesthetized with pentobarbital, transorally tracheostomized and intubated to the distal third of the esophagus with a saline-filled polyethylene tube (SOP: T-IIT-01-01).

The following lung function determinations will be conducted using SOPs Nos. T-IIT-02-01 through T-IIT-04-01 and T-IIT-07-01. (Note some measurements are collected by the BUXCO pulmonary function system but are not analyzed.):

1) Measurements obtained from the pressure volume curve: vital capacity (VCpv), total lung capacity (TLC), peak compliance (Cpk), and compliance at 0 to 10 cm H_2O (Cchord).

2) Measurements obtained during forced expiration: forced vital capacity (FVC), volume @ 50 msec of expiration (FEV50), volume @ 100 ms of expiration (FEV100), volume @ 200 ms of expiration (FEV200), volume @ 400 ms of expiration (FEV400), peak expiratory flow (PEXF), volume at PEXF (VPEXF), mean mid-expiratory flow (MMEXF), flow at 75% of FVC (FEF75), flow at 50% of FVC (FEF50), flow at 25% of FVC (FEF25), and flow at 10% of FVC (FEF10).

3) Measurements obtained from the gas dilution test: vital capacity (VC), total lung capacity (TLC), residual volume (RV), and diffusing capacity for CO (DLco).

4. Pulmonary Lavage (LAV):

4.1 Pulmonary Lavage, Total and Differential Cell Count:

The preassigned rats from each group will be sacrificed for collection of alveolar cells by tracheobronchial lavage (SOP: MBM 2.01) immediately following the measurement of the PF end points. Total and differential cell counts will be determined for the collected cells (SOP: MBM2.02 and MBM2.03).

4.2 Pulmonary Lavage Fluid Proteins:

The supernatant from the first several lung washes will be saved for protein determination. Lavage fluids will be assayed for protein by the method of Bradford (1976) Anal. Biochem. 72:248-254 (SOP: MBM6.02R1).

XIII. Statistical Methods:

According to contractual agreement with the government, Dr. Robert Gibbons, biostatistical consultant to the program, will conduct the statistical evaluation of the data using multivariate analysis of variance models for repeated measures and polynomial contrasts of log-transformed food consumption and body weight

data. Clinical pathology, hematology, organ/body weight, pulmonary lavage, and pulmonary function data will be evaluated using multivariate and univariate analyses of variance of log-transformed data. Statistical significances will be reported at the $p \leq 0.01$ and $p \leq 0.05$ levels.

XIV. Data Notebooks:

1. Contents: All original data will be maintained in notebooks and will include but not necessarily be limited to the following:

   a. Original signed protocol and all amendments
   b. Test substance information
   c. Animal receiving records
   d. Randomization procedures
   e. Animal housing and environmental conditions records
   f. Chemical generation and monitoring records
   g. Body weight records
   h. Mortality and clinical observations
   i. Food consumption records
   j. Clinical pathology records
   k. Necropsy and histopathology records
   l. Pulmonary lavage records
   m. Pulmonary function records

2. Storage:

   All original data and a copy of the final report will be kept in the IITRI Archives.

XV. Final Reports:

Following review and comments by the Sponsor, the required number of copies of the final report will be submitted.

XVI. Personnel:

Curricula vitae for all IITRI personnel involved in the study are on file at IITRI.

XVII. GLP Compliance:

The study will be conducted in compliance with EPA GLP requirements as specified in Part 792 of Title 40 of the Code of Federal Regulations and any later interpretations and revisions published by EPA. Quality Assurance inspections of phases of the study will be conducted as required.

XVIII. Changes or Revision of the Protocol:

This Protocol will be the controlling document for the conduct of this study. In the case of changes or discrepancies from the Protocol, these will be documented in Protocol Amendments or Deviations and submitted to the Sponsor (COTR).

Attachment A: Summary of Exposure and Experiment Dates, Animal Numbers, and Cage Locations.

Expo. Group Code	Endpoint Group	Aerosol Conc. (mg/m^3) PBL	Graphite	Chamber	Recov.	Exposure Start	Exposure End[a]	Experiment Date[b]	Animal Numbers	Cage Numbers
I	PATH	0	0	6	-	10/07/91	01/02/92	E1P-01/03/92	1-10	1-3
I	LAV/PF	0	0	6	-	10/07/91	01/02/92	E1L-01/03/92	11-15	3-4
I	LAV/PF	0	0	6	-	10/07/91	01/03/92[c]	E2L-01/04/92	16-20	5-6
IR	PATH	0	0	6	+	10/07/91	01/02/92	R1P-02/14/92	21-30	7-9
IR	LAV/PF	0	0	6	+	10/07/91	01/02/92	R1L-02/14/92	31-35	9-10
IR	LAV/PF	0	0	6	+	10/07/91	01/03/92	R2L-02/15/92	36-40	11-12
II	PATH	250	100	5	-	10/07/91	01/02/92	E1P-01/03/92	41-50	13-15
II	LAV/PF	250	100	5	-	10/07/91	01/02/92	E1L-01/03/92	51-55	15-16
II	LAV/PF	250	100	5	-	10/07/91	01/03/92[c]	E2L-01/04/92	56-60	17-18
IIR	PATH	250	100	5	+	10/07/91	01/02/92	R1P-02/14/92	61-70	19-21
IIR	LAV/PF	250	100	5	+	10/07/91	01/02/92	R1L-02/14/92	71-75	21-22
IIR	LAV/PF	250	100	5	+	10/07/91	01/03/92	R2L-02/15/92	76-80	23-24
III	PATH	500	100	3	-	10/07/91	01/02/92	E1P-01/03/92	81-90	25-27
III	LAV/PF	500	100	3	-	10/07/91	01/02/92	E1L-01/03/92	91-95	27-28
III	LAV/PF	500	100	3	-	10/07/91	01/03/92[c]	E2L-01/04/92	96-100	29-30
IIIR	PATH	500	100	3	+	10/07/91	01/02/92	R1P-02/14/92	101-110	31-33
IIIR	LAV/PF	500	100	3	+	10/07/91	01/02/92	R1L-02/14/92	111-115	33-34
IIIR	LAV/PF	500	100	3	+	10/07/91	01/03/92	R2L-02/15/92	116-120	35-36
IV	PATH	500	200	1	-	10/07/91	01/02/92	E1P-01/03/92	121-130	37-39
IV	LAV/PF	500	200	1	-	10/07/91	01/02/92	E1L-01/03/92	131-135	39-40
IV	LAV/PF	500	200	1	-	10/07/91	01/03/92[c]	E2L-01/04/92	136-140	41-42
IVR	PATH	500	200	1	+	10/07/91	01/02/92	R1P-02/14/92	141-150	43-45
IVR	LAV/PF	500	200	1	+	10/07/91	01/02/92	R1L-02/14/92	151-155	45-46
IVR	LAV/PF	500	200	1	+	10/07/91	01/03/92	R2L-02/15/92	156-160	47-48
V	PATH	1000	200	2	-	10/07/91	01/02/92	E1P-01/03/92	161-170	49-51
V	LAV/PF	1000	200	2	-	10/07/91	01/02/92	E1L-01/03/92	171-175	51-52
V	LAV/PF	1000	200	2	-	10/07/91	01/03/92[c]	E2L-01/04/92	176-180	53-54
VR	PATH	1000	200	2	+	10/07/91	01/02/92	R1P-02/14/92	181-190	55-57
VR	LAV/PF	1000	200	2	+	10/07/91	01/02/92	R1L-02/14/92	191-195	57-58
VR	LAV/PF	1000	200	2	+	10/07/91	01/03/92	R2L-02/15/92	196-200	59-60

[a] Exposure End Days are staggered to fall on Thursday and Friday in the last exposure week.

[b] E = Assay days 1 (and 2 as applicable) for the EXP (within 24 hr of the last exposure) end point timing for PATH (P) and LAV/PF (L); R = Assay days 1 (and 2 as applicable) for the REC (after a six-week recovery period) end point timing.

[c] One additional exposure (compared to E1, R1 or R2 assay groups) in the last exposure week prior to assay on Saturday.

PROTOCOL AMENDMENT 1

Study Title: **THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS**

1. Change:
   - o Asterisks are added after the exposure end dates in Attachment A (Summary of Exposure and Experiment Dates, Animal Numbers, and Cage Locations) for the LAV/PF rats scheduled for the 2/15/92 recovery experiment date.
   - o The footnote in Attachment A which defines the asterisk is changed to read "* One additional exposure (compared to E1 or R1 assay groups) in the last exposure week."

   Reason: Correction of previous inconsistency between exposure end dates and the description of which animals would receive one additional exposure.

2. Change: The first two paragraphs of Section XII.3. (Pulmonary Function) are changed to read as follows:

   The pulmonary function parameters will be measured using an acrylic plethysmograph (BUXCO Electronics, Inc.) equipped to measure airflow and volume in anesthetized animals.

   Each test animal (which will also be used later for the LAV measurements) will be weighed (tattoo I.D. also recorded), anesthetized with pentobarbital and trans-orally tracheostomized (SOP: T-IIT-01-01).

   Reason: The changes were requested by Dr. Tepper, the pulmonary physiology consultant, and were not received before the protocol was signed.

Approval:

Study Director: Jeannie Bradof — Jeannie Bradof — Date: 12/19/91

Prin. Invest./ Manager, Inhalation Tox.: Catherine Aranyi — Catherine Aranyi — Date: 12/19/91

Manager, Quality Assurance: Ronald Boyne — Ronald Boyne — Date: 12-19-91

Sponsor (COTR): Jack L. Dacre — Dr. Jack Dacre — Date: 1-13-92

Attachment A: Summary of Exposure and Experiment Dates, Animal Numbers, and Cage Locations (Revised).

Expo. Group Code	Endpoint Group	Aerosol Conc. (mg/m^3) PBL	Graphite	Chamber	Recov.	Exposure Start	Exposure End[a]	Experiment Date[b]	Animal Numbers	Cage Numbers
I	PATH	0	0	6	-	10/07/91	01/02/92	E1P-01/03/92	1-10	1-3
I	LAV/PF	0	0	6	-	10/07/91	01/02/92	E1L-01/03/92	11-15	3-4
I	LAV/PF	0	0	6	-	10/07/91	01/03/92*	E2L-01/04/92	16-20	5-6
IR	PATH	0	0	6	+	10/07/91	01/02/92	R1P-02/14/92	21-30	7-9
IR	LAV/PF	0	0	6	+	10/07/91	01/02/92	R1L-02/14/92	31-35	9-10
IR	LAV/PF	0	0	6	+	10/07/91	01/03/92*	R2L-02/15/92	36-40	11-12
II	PATH	250	100	5	-	10/07/91	01/02/92	E1P-01/03/92	41-50	13-15
II	LAV/PF	250	100	5	-	10/07/91	01/02/92	E1L-01/03/92	51-55	15-16
II	LAV/PF	250	100	5	-	10/07/91	01/03/92*	E2L-01/04/92	56-60	17-18
IIR	PATH	250	100	5	+	10/07/91	01/02/92	R1P-02/14/92	61-70	19-21
IIR	LAV/PF	250	100	5	+	10/07/91	01/02/92	R1L-02/14/92	71-75	21-22
IIR	LAV/PF	250	100	5	+	10/07/91	01/03/92*	R2L-02/15/92	76-80	23-24
III	PATH	500	100	3	-	10/07/91	01/02/92	E1P-01/03/92	81-90	25-27
III	LAV/PF	500	100	3	-	10/07/91	01/02/92	E1L-01/03/92	91-95	27-28
III	LAV/PF	500	100	3	-	10/07/91	01/03/92*	E2L-01/04/92	96-100	29-30
IIIR	PATH	500	100	3	+	10/07/91	01/02/92	R1P-02/14/92	101-110	31-33
IIIR	LAV/PF	500	100	3	+	10/07/91	01/02/92	R1L-02/14/92	111-115	33-34
IIIR	LAV/PF	500	100	3	+	10/07/91	01/03/92*	R2L-02/15/92	116-120	35-36
IV	PATH	500	200	1	-	10/07/91	01/02/92	E1P-01/03/92	121-130	37-39
IV	LAV/PF	500	200	1	-	10/07/91	01/02/92	E1L-01/03/92	131-135	39-40
IV	LAV/PF	500	200	1	-	10/07/91	01/03/92*	E2L-01/04/92	136-140	41-42
IVR	PATH	500	200	1	+	10/07/91	01/02/92	R1P-02/14/92	141-150	43-45
IVR	LAV/PF	500	200	1	+	10/07/91	01/02/92	R1L-02/14/92	151-155	45-46
IVR	LAV/PF	500	200	1	+	10/07/91	01/03/92*	R2L-02/15/92	156-160	47-48
V	PATH	1000	200	2	-	10/07/91	01/02/92	E1P-01/03/92	161-170	49-51
V	LAV/PF	1000	200	2	-	10/07/91	01/02/92	E1L-01/03/92	171-175	51-52
V	LAV/PF	1000	200	2	-	10/07/91	01/03/92*	E2L-01/04/92	176-180	53-54
VR	PATH	1000	200	2	+	10/07/91	01/02/92	R1P-02/14/92	181-190	55-57
VR	LAV/PF	1000	200	2	+	10/07/91	01/02/92	R1L-02/14/92	191-195	57-58
VR	LAV/PF	1000	200	2	+	10/07/91	01/03/92*	R2L-02/15/92	196-200	59-60

[a] Exposure End Days are staggered to fall on Thursday and Friday in the last exposure week.

[b] E = Assay days 1 (and 2 as applicable) for the EXP (within 24 hr of the last exposure) end point timing for PATH (P) and LAV/PF (L); R = Assay days 1 (and 2 as applicable) for the REC (after a six-week recovery period) end point timing.

* One additional exposure (compared to E1 and R1 assay groups) in the last exposure week.

CONTRACT NO.: DAMD17-89-C-9043
IITRI PROJECT NO.: L06234

INHALATION TOXICITY OF SINGLE MATERIALS AND MIXTURES: PHASE IV - THIRTEEN-WEEK INHALATION TOXICITY STUDY WITH AEROSOL MIXTURES OF FOG OIL AND GRAPHITE PARTICLES IN F344/N MALE RATS

PART TWO

STATISTICAL OVERVIEW OF THE RESULTS

Prepared by:

Robert D. Gibbons

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July 14, 1992

Supported by:

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
FORT DETRICK, FREDERICK, MARYLAND 21702-5012

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PART TWO

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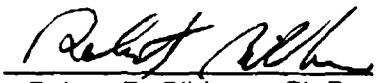

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PART TWO
TABLE OF CONTENTS

1 Introduction

The purpose of Part Two of this report is to provide a review of the results of statistical analysis of data presented in the Part One Technical Report. The report begins by presenting an overview of the statistical methods used in the analysis of the various sets of outcome measures (*i.e.*, hematology, clinical chemistry, etc.), followed by a summary of significant differences from control for the four exposure groups at exposure and recovery sacrifices, respectively.

2 Statistical Methodology

Multivariate analysis of variance models (Bock, 1975) were used to analyze each set of variables (*i.e.*, hematology, pulmonary lavage, hematology differentials, clinical chemistry, and pulmonary function). Univariate analysis of variance (Winer, 1971) was used to analyze relative lung weights. Multivariate analysis of variance for repeated measurements (Bock, 1975), was used to analyze repeated body weight gain and food consumption measurements. Prior to analysis, natural log transformation of the data was performed on these variables to better approximate the normality assumption of the statistical model. To better understand the potential for recovery from any effects observed following the exposure period, separate analyses were performed for exposure sacrifice and recovery sacrifice animals. This departs somewhat from previous phase analyses due to the confirmatory nature of this study, which was designed on the basis of the results from earlier phases. The four exposure groups were PBL=250 mg/m^3 and graphite=100 mg/m^3, PBL=500 mg/m^3 and graphite=100 mg/m^3, PBL=500 mg/m^3 and graphite=200 mg/m^3, and PBL=1000 mg/m^3 and graphite=200 mg/m^3.

In the presence of a significant multivariate test statistic, univariate ANOVA was performed for each of the individual biological end points in that category (*e.g.*, clinical chemistry). In the presence of a significant univariate result, individual comparisons to control were examined. These analyses were performed in parallel for exposure and recovery sacrifice animals.

Multivariate analysis of variance models (Bock, 1975) were used to analyze the body weight gains. For the analysis of the post-exposure period, weekly body weight gain values for days 5 through 89 were examined and for the analysis of the post-recovery period days 96 through 131 were examined. A multivariate analysis of variance for repeated measures

was then performed, utilizing orthogonal polynomial contrasts, to examine for constant and linear trend effects over time.

Multivariate analysis of variance models for repeated measures were also used to analyze food consumption. In these analyses, polynomial contrasts were utilized to test for constant effects across time as well as for linear trends across time.

3 Results

Probability values and direction of difference (*i.e.*, + = exposed greater than control and − = less than control) are reported in Table 1 for all statistically significant results at either post-exposure or recovery sacrifice periods. Probability values next to each end-point category (*e.g.*, hematology) represent the probability for the multivariate test statistic. Inspection of Table 1 reveals the following overall results.

1. Body weight gains were relatively unaffected by treatment.

2. Clinical chemistry measures exhibited several exposure related effects, most of which returned to control levels following the recovery period.

3. Differential counts (WBC and NEUT) exhibited exposure-related increases relative to controls following the recovery period.

4. Hematology measures (excluding the effect for WBC as previously noted for differentials) did not exhibit a significant multivariate effect.

5. Relative lung weights were increased in all exposure groups relative to controls at both post-exposure and recovery sacrifice periods.

6. Pulmonary Lavage measures were consistently different from controls for all treatment groups at both post-exposure and recovery sacrifice periods.

7. Food consumption was greater for all treatment groups relative to controls during the recovery period only.

8. Several Pulmonary Function measures were significantly decreased in all treatment groups relative to controls, the majority of which did not exhibit recovery.

Specific details for each end-point category are now provided.

3.1 Body Weight Gain

A significant overall body weight gain effect (i.e., constant difference) was observed for exposure sacrifice animals ($p < .012$). Post-hoc comparisons revealed significantly increased body weight gain for PBL=500 + graphite=100 relative to controls. Summary statistics are presented in Table 2.

3.2 Clinical Chemistry

An overall multivariate main effect of group was found for post-exposure sacrifice animals ($p < .009$) but not following recovery. BUN values were significantly increased in post-exposure PBL=250 + graphite=100 ($p < .021$), and PBL=500 + graphite=200 ($p < .026$) animals relative to controls. ALT values were significantly decreased in post-exposure PBL=500 + graphite=100 ($p < .043$), and PBL=1000 + graphite=200 ($p < .032$) animals relative to controls. ALBG values were significantly decreased in post-exposure PBL=1000 + graphite=200 ($p < .020$) animals relative to controls. TP values were significantly decreased in post-exposure PBL=500 + graphite=200 ($p < .004$), and PBL=1000 + graphite=200 ($p < .004$) animals relative to controls. CK values were significantly increased in post-exposure PBL=500 + graphite=200 ($p < .026$) animals relative to controls. For TBA values, the overall F-statistic approached significance ($p < .065$). TBA values were significantly decreased in post-exposure, PBL=500 + graphite=100 ($p < .025$), and PBL=1000 + graphite=200 ($p < .011$) animals relative to controls, and approached significance for PBL=250 + graphite=100 ($p < .054$). In the absence of a significant univariate main effect, however, these significant post-hoc comparisons for TBA should be interpreted with extreme caution, since they are consistent with chance expectations at the 5% level. CHOL values were significantly decreased in post-exposure PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. CA values were significantly decreased in post-exposure PBL=250 + graphite=100 ($p < .036$), PBL=500 + graphite=200 ($p < .003$), and PBL=1000 + graphite=200 ($p < .010$) animals relative to controls. Finally, although the multivariate test was not significant, a significant univariate statistic was found for recovery sacrifice PHOS levels in PBL=1000 + graphite=200 ($p < .002$) animals relative to controls. This result is consistent with chance expectations as indicated by the nonsignificant multivariate result. Summary statistics are provided in Table 3.

3.3 Hematology

The overall multivariate main effect of group was not significant for either post-exposure or recovery sacrifice animals. Univariate test statistics were significant for WBC levels (reported under Differentials) and decreased values of PLT were found for post-exposure sacrifice PBL=500 + graphite=200 ($p < .036$) animals relative to controls. This result is consistent with chance expectations as indicated by the nonsignificant multivariate result. Summary statistics are displayed in Table 4.

3.4 Differential Counts

An overall multivariate main effect of group was found for recovery sacrifice animals ($p < .001$) but not for post-exposure sacrifice animals. Following the recovery period, WBC values were increased in PBL=250 + graphite=100 ($p < .010$), PBL=500 + graphite=100 ($p < .029$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Similarly, following the recovery period, NEUT values were increased in PBL=250 + graphite=100 ($p < .009$), PBL=500 + graphite=100 ($p < .001$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Summary statistics are displayed in Table 5.

3.5 Relative Lung to Body Weight Ratios

An overall multivariate main effect of group was found for post-exposure sacrifice animals ($p < .001$) and for recovery sacrifice animals ($p < .001$). Following the exposure period, relative lung weights were increased in PBL=250 + graphite=100 ($p < .005$), PBL=500 + graphite=100 ($p < .001$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Similarly, following the recovery period, relative lung weights were increased in PBL=250 + graphite=100 ($p < .001$), PBL=500 + graphite=100 ($p < .001$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Summary statistics are displayed in Table 6.

3.6 Pulmonary Lavage

An overall multivariate main effect of group was found for both post-exposure sacrifice animals ($p < .001$) and recovery sacrifice animals ($p < .001$). Following the exposure period,

all treated groups had significantly increased viable cells, total cells and lavage fluid protein ($p < .001$). Percent viable cells was significantly decreased in PBL=500 + graphite=100 ($p < .002$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls and approached significance for PBL=250 + graphite=100 ($p < .053$). Percent macrophages was significantly decreased in PBL=500 + graphite=200 ($p < .001$) animals relative to controls, and percent neutrophils was significantly increased in PBL=500 + graphite=200 ($p < .001$) animals relative to controls.

Following the recovery period, all treated groups had significantly increased viable cells and total cells ($p < .001$). Lavage fluid protein was also significantly increased in PBL=250 + graphite=100 ($p < .002$), PBL=500 + graphite=100 ($p < .011$), PBL=500 + graphite=200 ($p < .003$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Percent viable cells was significantly decreased in PBL=500 + graphite=100 ($p < .008$), PBL=500 + graphite=200 ($p < .005$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Percent macrophages was significantly decreased in PBL=250 + graphite=100 ($p < .001$), PBL=500 + graphite=100 ($p < .006$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls, and percent neutrophils was significantly increased in PBL=250 + graphite=100 ($p < .001$), PBL=500 + graphite=100 ($p < .011$), PBL=500 + graphite=200 ($p < .001$), and PBL=1000 + graphite=200 ($p < .001$) animals relative to controls. Summary statistics are displayed in Table 7.

3.7 Food Consumption

Food consumption was only measured in recovery sacrifice animals. During the exposure period, no significant treatment-related differences in food consumption were observed. During the recovery period, however, a significant overall effect (*i.e.*, averaging over time during the recovery period (constant), see Table 1) was observed ($p < .001$). Post-hoc comparisons revealed significantly increased food consumption averaging over the recovery period for all groups relative to controls. Inspection of the summary statistics in Table 8 reveal that treated animals consumed more than controls during the recovery period.

3.8 Pulmonary Function

Given the large number of end points, the multivariate statistics have limited power. The multivariate statistic was significant for the post-exposure sacrifice animals ($p < .036$), but

not for the post-recovery sacrifice animals ($p < .366$), despite consistent significant univariate results which we will interpret (see Table 1). Significant treatment-related decreases in pulmonary function were observed for VC, CPK, CCHORD, FVC, FEV200, and FEV400 for both post-exposure and post-recovery sacrifice animals (see Table 1). Inspection of probability values in Table 1 and summary statistics in Table 9, reveal that the effect is increasing with concentration (but almost all treatment versus control comparisons are significant) and is significant but less pronounced following the recovery period. In addition TLC levels were significantly decreased in all treated animals relative to controls following the exposure period but not after the recovery period.

When these pulmonary function data were adjusted for body weight, the results were almost identical to the results for the unadjusted data. In general, however, probability values were somewhat smaller, all treatment groups were significantly decreased relative to controls for the previously reported measures, and all post-exposure sacrifice animals also exhibited significantly decreased FEV100 levels relative to controls, but this effect was not observed following the recovery period.

4 Summary

These results indicate that exposure to particularly the higher concentrations of PBL and graphite produced significant changes in several clinical chemistry end points, which returned to normal levels following the recovery period. In addition, exposure to all exposure combinations produced significant increases in relative lung weights which did not exhibit any recovery. WBC and NEUT differential counts exhibited significant increases in all exposure groups following the recovery period but not at the post-exposure sacrifice. Pulmonary lavage measures exhibited consistent differences from controls for all treatment groups, and these effects did not exhibit recovery. Several pulmonary function measures exhibited significant differences from control for all treatment groups, the majority of which did not exhibit recovery (*i.e.*, VC, CPK, CCHORD, FVC, FEV200, and FEV400 did not exhibit recovery, but TLC did). Adjustment for body weight revealed quite similar results, with the addition of a significant post-exposure effect for FEV100 which exhibited recovery. No consistent exposure-related effects on body weight or food consumption were observed.

References

[1] Bock, R. D. *Multivariate statistical methods in behavioral research*. New York: McGraw-Hill, 1975.

[2] Winer, B. J. *Statistical principles in experimental design*. 2nd edition. New York: McGraw-Hill, 1971.

PART TWO

ATTACHMENT 1

TABLES

PART TWO
ATTACHMENT 1

LIST OF TABLES

TABLE 1

SUMMARY OF STATISTICALLY SIGNIFICANT RESULTS

VARIABLE	EXPOSURE PERIOD GROUP					RECOVERY PERIOD GROUP				
	F	2-1	3-1	4-1	5-1	F	2-1	3-1	4-1	5-1
BODY WT GAIN										
CONSTANT	.012		.04+							
LINEAR										
CLIN CHEM	**.009**					**.202**				
BUN	.021	.021+		.026+						
CREA										
ALP										
ALT	.048		.043-		.032-					
ALBG	.050				.020-					
TP	.002			.004-	.004-					
CK	.004			.026+						
TBA										
SDH										
GLU										
CHOL	.001			.001-	.001-					
TRIG										
CA	.011	.036-		.003-	.010-					
PHOS						.020				.002-
DIFF. COUNTS	**.530**					**.001**				
WBC						.002	.010+	.029+	.001+	.001+
NRBC										
NEUT						.001	.009+	.001+	.001+	.001+
LYMPH										
MONO										
EOS										
HEMATOLOGY	**.183**					**.197**				
WBC						.002	.010+	.029+	.001+	.001+
RBC										
HGB										
HCT										
MCV										
MCH										
MCHC										
PLT	.043			.036-						
LUNG/BW	.001	.005+	.001+	.001+	.001+	.001	.001+	.001+	.001+	.001+
LAVAGE	**.001**					**.001**				
VIABLE	.001	.001+	.001+	.001+	.001+	.001	.001+	.001+	.001+	.001+
TOTAL	.001	.001+	.001+	.001+	.001+	.001	.001+	.001+	.001+	.001+
% VIABLE	.001		.002-	.001-	.001-	.007		.008-	.005-	.001-
% MACRO	.014			.001-		.001	.001-	.006-	.001-	.001-
% NEUT	.014			.001+		.001	.001+	.011+	.001+	.001+
PROTEIN	.001	.001+	.001+	.001+	.001+	.001	.002+	.011+	.003+	.001+
VIABLE	.001	.001+	.001+	.001+	.001+	.001	.001+	.001+	.001+	.001+
FOOD CONSUMPTION										
CONSTANT						.001	.001+	.001+	.001+	.001+
LINEAR										

F = PROBABILITY FOR GROUP MAIN EFFECT
2 - 1 = PBL=250+GRAPHITE=100 - CONTROL
3 - 1 = PBL=500+GRAPHITE=100 - CONTROL
4 - 1 = PBL=500+GRAPHITE=200 - CONTROL
5 - 1 = PBL=1000+GRAPHITE=200 - CONTROL
.001- = SIGNIFICANT DIFFERENCE $p < .001$, EXPOSED < CONTROL
.001+ = SIGNIFICANT DIFFERENCE $p < .001$, EXPOSED > CONTROL
.001 = PROBABILITY FOR MULTIVARIATE TEST

TABLE 1 - CONTINUED

SUMMARY OF STATISTICALLY SIGNIFICANT RESULTS

VARIABLE	EXPOSURE PERIOD					RECOVERY PERIOD				
	GROUP					GROUP				
	F	2-1	3-1	4-1	5-1	F	2-1	3-1	4-1	5-1
PULM. FUNC.	**.036**					**.366**				
TLC	.007	.040-	.011-	.001-	.003-					
RV										
DLCO										
VC	.007	.033-	.010-	.001-	.002-	.018	.022-	.026-		.001-
CPK	.002		.004-	.001-	.001-	.006	.007-	.011-	.020-	.001-
CCHORD	.001	.020-	.004-	.001-	.001-	.038	.013-	.015-		.006-
FVC	.012	.038-	.008-	.001-	.008-	.026	.024-	.026-	.049-	.002-
FEV50										
FEV100										
FEV200	.004	.015-	.004-	.001-	.001-	.026	.029-	.024-	.026-	.002-
FEV400	.010	.023-	.007-	.001-	.006-	.022	.025-	.021-	.027-	.001-
PEF										
FEF75										
FEF50										
FEF25										
PF ADJ BW	**.015**					**.156**				
TLC	.006	.014-	.004-	.001-	.002-					
RV										
DLCO										
VC	.006	.012-	.005-	.001-	.002-	.010	.013-	.014-	.022-	.001-
CPK	.003	.031-	.003-	.001-	.002-	.005	.006-	.008-	.011-	.001-
CCHORD	.001	.006-	.002-	.001-	.001-	.028	.010-	.011-	.036-	.004-
FVC	.008	.008-	.003-	.001-	.008-	.013	.015-	.015-	.016-	.001-
FEV50										
FEV100	.023	.009-	.007-	.009-	.008-					
FEV200	.002	.003-	.001-	.001-	.001-	.010	.016-	.011-	.006-	.001-
FEV400	.005	.006-	.002-	.001-	.005-	.010	.014-	.011-	.007-	.001-
PEF										
FEF75										
FEF50										
FEF25										

PF ADJ BW - PULMONARY FUNCTION ADJUSTED FOR BODY WEIGHT
F = PROBABILITY FOR GROUP MAIN EFFECT
2 - 1 = PBL=250+GRAPHITE=100 - CONTROL
3 - 1 = PBL=500+GRAPHITE=100 - CONTROL
4 - 1 = PBL=500+GRAPHITE=200 - CONTROL
5 - 1 = PBL=1000+GRAPHITE=200 - CONTROL
.001- = SIGNIFICANT DIFFERENCE $p < .001$, EXPOSED < CONTROL
.001+ = SIGNIFICANT DIFFERENCE $p < .001$, EXPOSED > CONTROL
.001 = PROBABILITY FOR MULTIVARIATE TEST

TABLE 2
BODY WEIGHT GAIN ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns of All Animals by Group

GROUP	BWG5	BWG12	BWG19	BWG26	BWG33	BWG40	BWG47
Control							
mean	12.85	39.05	57.10	77.45	95.83	110.50	124.28
sd	2.84	5.81	8.39	10.51	12.71	14.72	16.63
n	40	40	40	40	40	40	40
PBL=250 Graphite=100							
mean	11.75	38.08	56.72	78.43	95.68	113.08	128.02
sd	3.76	4.77	7.74	9.36	11.18	12.65	13.74
n	40	40	40	40	40	40	40
PBL=500 Graphite=100							
mean	12.57	40.13	59.65	81.05	99.30	117.25	131.62
sd	3.05	5.92	8.14	10.37	12.57	13.68	15.42
n	40	40	40	40	40	40	40
PBL=500 Graphite=200							
mean	9.87	36.47	57.63	79.00	95.90	112.48	124.75
sd	9.20	11.11	10.64	11.99	12.80	14.12	15.47
n	40	40	40	40	40	40	40
PBL=1000 Graphite=200							
mean	9.45	35.65	56.53	76.10	92.77	107.65	119.57
sd	4.12	6.24	8.52	10.70	12.66	14.55	15.07
n	40	40	40	40	40	40	40

TABLE 2 - Continued
BODY WEIGHT GAIN ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns of All Animals by Group

GROUP	BWG54	BWG61	BWG68	BWG75	BWG82	BWG89
Control						
mean	137.78	151.85	162.15	174.78	183.28	194.53
sd	16.96	18.64	19.89	20.41	20.79	21.69
n	40	40	40	40	40	40
PBL=250 Graphite=100						
mean	143.65	155.55	167.65	178.73	186.72	197.73
sd	14.75	15.82	16.25	17.08	19.59	18.34
n	40	40	40	40	40	40
PBL=500 Graphite=100						
mean	148.45	157.55	171.85	183.93	189.78	203.30
sd	17.40	19.56	18.45	18.71	20.58	19.79
n	40	40	40	40	40	40
PBL=500 Graphite=200						
mean	141.07	152.58	163.05	174.60	183.27	194.30
sd	16.91	17.40	18.01	18.58	20.00	19.81
n	40	40	40	40	40	40
PBL=1000 Graphite=200						
mean	135.07	144.73	155.38	167.65	177.53	188.08
sd	15.83	15.81	16.30	16.66	17.82	18.90
n	40	40	40	40	40	40

TABLE 2 - Continued
BODY WEIGHT GAIN ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns of Recovery Animals by Group

GROUP	BWG96	BWG103	BWG110	BWG117	BWG124	BWG131
Control						
mean	193.10	201.25	205.25	213.30	220.60	226.70
sd	19.28	19.01	20.36	19.78	20.13	21.03
n	20	20	20	20	20	20
PBL=250 Graphite=100						
mean	199.80	208.70	216.35	223.20	233.20	238.70
sd	14.72	16.46	16.95	17.92	18.53	17.97
n	20	20	20	20	20	20
PBL=500 Graphite=100						
mean	207.95	216.85	223.05	231.50	238.95	244.00
sd	22.20	21.70	21.74	22.57	23.84	25.52
n	20	20	20	20	20	20
PBL=500 Graphite=200						
mean	204.75	214.60	221.35	230.00	237.10	243.80
sd	20.00	20.80	21.49	23.18	24.92	23.74
n	20	20	20	20	20	20
PBL=1000 Graphite=200						
mean	196.10	208.00	213.85	223.15	229.85	236.10
sd	19.52	20.96	21.07	21.60	23.53	24.27
n	20	20	20	20	20	20

TABLE 3
CLINICAL CHEMISTRY ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	CK	ALP	ALT	BUN	CREA	GLU	TP
Post-Exp	Control							
	mean	137.60	300.60	83.40	15.83	.64	189.61	7.12
	sd	53.11	32.67	39.33	1.75	.08	34.76	.23
	n	10	10	10	10	10	10	10
	PBL=250 Graphite=100							
	mean	156.40	306.40	83.80	17.31	.66	157.07	7.01
	sd	55.54	26.31	42.00	1.05	.08	35.42	.19
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=100							
	mean	164.50	299.00	55.10	15.62	.64	173.52	7.14
	sd	82.62	30.92	12.96	1.37	.06	33.43	.30
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=200							
	mean	225.90	300.40	85.40	17.29	.69	178.98	6.81
	sd	135.63	27.81	48.56	1.62	.14	40.79	.26
	n	10	10	10	10	10	10	10
	PBL=1000 Graphite=200							
	mean	95.20	300.50	53.20	16.76	.62	172.90	6.81
	sd	22.79	26.51	7.15	1.38	.06	53.07	.13
	n	10	10	10	10	10	10	10
Post-Rec	Control							
	mean	155.70	303.20	79.50	17.27	.73	182.42	7.19
	sd	141.54	36.61	30.90	1.45	.10	37.60	.23
	n	10	10	10	10	10	10	10
	PBL=250 Graphite=100							
	mean	122.10	310.80	74.20	17.50	.66	165.84	7.21
	sd	59.34	22.05	28.70	1.39	.08	23.02	.25
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=100							
	mean	152.90	301.80	70.30	18.44	.70	160.81	7.19
	sd	129.47	36.58	21.86	1.77	.06	21.52	.22
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=200							
	mean	125.40	287.80	61.20	17.65	.69	173.75	7.02
	sd	80.75	26.49	19.75	1.68	.07	45.70	.37
	n	10	10	10	10	10	10	10
	PBL=1000 Graphite=200							
	mean	117.60	307.40	61.40	17.82	.69	155.45	7.09
	sd	51.83	24.02	11.88	1.65	.06	41.92	.10
	n	10	10	10	10	10	10	10

TABLE 3 - Continued
CLINICAL CHEMISTRY ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	ALBG	CHOL	TRIG	CA	TBA	PHOS	SDH
Post-Exp	Control							
	mean	4.27	43.76	183.78	12.13	21.81	9.52	56.51
	sd	.12	2.77	29.63	.52	8.21	1.31	55.95
	n	10	10	10	10	10	10	10
	PBL=250 Graphite=100							
	mean	4.24	42.88	188.30	11.75	16.28	8.29	49.35
	sd	.15	4.54	44.72	.35	4.51	1.16	34.07
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=100							
	mean	4.29	41.06	176.61	12.03	15.18	8.64	26.85
	sd	.16	2.19	27.39	.30	2.10	.67	11.51
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=200							
	mean	4.17	38.21	180.52	11.59	20.09	8.52	61.52
	sd	.13	3.95	24.24	.28	10.69	1.82	54.49
	n	10	10	10	10	10	10	10
	PBL=1000 Graphite=200							
	mean	4.12	38.33	178.04	11.66	14.64	9.01	24.69
	sd	.15	2.58	42.70	.41	2.86	1.32	7.27
	n	10	10	10	10	10	10	10
Post-Rec	Control							
	mean	4.41	47.17	168.02	11.79	20.67	7.78	43.65
	sd	.13	5.50	21.34	.38	7.53	1.28	26.69
	n	10	10	10	10	10	10	10
	PBL=250 Graphite=100							
	mean	4.34	45.77	171.68	11.88	15.79	7.05	38.58
	sd	.15	3.53	18.66	.23	3.98	.68	22.93
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=100							
	mean	4.31	45.72	162.31	11.73	16.00	6.97	36.39
	sd	.14	3.9[illegible]	25.27	.25	4.42	.95	20.60
	n	10	10	10	10	10	10	10
	PBL=500 Graphite=200							
	mean	4.21	44.80	169.86	11.60	16.95	7.58	27.63
	sd	.24	3.43	27.74	.41	6.98	1.46	20.81
	n	10	10	10	10	10	10	10
	PBL=1000 Graphite=200							
	mean	4.34	43.19	161.66	11.63	15.52	6.31	28.68
	sd	.10	3.68	15.10	.28	1.64	.92	9.99
	n	10	10	10	10	10	10	10

TABLE 4
HEMATOLOGY ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	WBC	RBC	HGB	HCT	MCV	MCH	MCHC	PLT
Post-Exp	Control								
	mean	8.44	9.12	16.16	44.90	49.23	17.73	36.01	781.70
	sd	1.48	.42	.52	2.10	.54	.41	.74	36.72
	n	10	10	10	10	10	10	10	10
	PBL=250 Graphite=100								
	mean	8.38	9.01	15.78	44.30	49.17	17.53	35.64	782.20
	sd	1.56	.39	.51	1.97	.56	.39	.76	51.27
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=100								
	mean	8.62	9.17	16.14	44.87	48.95	17.62	36.01	803.40
	sd	1.06	.36	.45	1.85	.48	.45	.87	28.84
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=200								
	mean	8.78	9.13	16.00	44.84	49.13	17.53	35.69	739.11
	sd	1.64	.18	.54	.77	.51	.56	1.00	68.70
	n	9	9	9	9	9	9	9	9
	PBL=1000 Graphite=200								
	mean	9.67	8.85	15.61	43.36	49.03	17.66	36.02	769.10
	sd	.98	.46	.64	2.00	.38	.33	.62	34.66
	n	10	10	10	10	10	10	10	10
Post-Rec	Control								
	mean	7.61	8.72	15.70	43.60	50.00	18.01	36.02	771.50
	sd	1.04	.21	.32	.95	.52	.32	.35	47.68
	n	10	10	10	10	10	10	10	10
	PBL=250 Graphite=100								
	mean	8.75	8.89	15.87	44.15	49.65	17.86	35.96	773.80
	sd	.87	.37	.50	1.72	.52	.41	.64	39.28
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=100								
	mean	8.60	8.83	15.79	43.91	49.72	17.88	35.95	747.00
	sd	.73	.19	.44	1.10	.42	.23	.31	45.22
	n	8	8	8	8	8	8	8	8
	PBL=500 Graphite=200								
	mean	9.31	8.63	15.49	42.96	49.76	17.94	36.08	793.89
	sd	1.25	.38	.64	1.80	.37	.17	.35	56.61
	n	9	9	9	9	9	9	9	9
	PBL=1000 Graphite=200								
	mean	9.34	8.89	15.85	43.97	49.48	17.83	36.06	769.50
	sd	1.11	.25	.44	1.48	.50	.24	.39	38.20
	n	10	10	10	10	10	10	10	10

TABLE 5
HEMATOLOGY DIFFERENTIAL COUNT ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	WBC	NRBC	NEUT	LYMPH	MONO	EOS	BASO	IMNEUT
Post-Exp	Control								
	mean	8.44	.07	1.80	6.30	.29	.06	0.00	0.00
	sd	1.48	.12	.41	1.34	.13	.04	0.00	0.00
	n	10	10	10	10	10	10	10	10
	PBL=250 Graphite=100								
	mean	8.38	.02	2.02	6.04	.27	.05	0.00	0.00
	sd	1.56	.05	.63	1.15	.12	.05	0.00	0.00
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=100								
	mean	8.62	.07	2.02	6.26	.27	.08	0.00	0.00
	sd	1.06	.05	.25	1.12	.12	.05	0.00	0.00
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=200								
	mean	8.78	.01	2.00	6.44	.28	.05	0.00	0.00
	sd	1.64	.03	.70	.95	.14	.07	0.00	0.00
	n	9	9	9	9	9	9	9	9
	PBL=1000 Graphite=200								
	mean	9.67	.03	2.22	6.99	.39	.08	0.00	0.00
	sd	.98	.04	.38	.82	.11	.07	0.00	0.00
	n	10	10	10	10	10	10	10	10
Post-Rec	Control								
	mean	7.61	.06	1.61	5.48	.47	.06	0.00	0.00
	sd	1.04	.04	.33	.75	.12	.08	0.00	0.00
	n	10	10	10	10	10	10	10	10
	PBL=250 Graphite=100								
	mean	8.75	.06	2.11	6.04	.52	.09	0.00	0.00
	sd	.87	.06	.33	.60	.20	.07	0.00	0.00
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=100								
	mean	8.60	.07	2.43	5.57	.50	.12	0.00	0.00
	sd	.73	.03	.52	.36	.11	.12	0.00	0.00
	n	8	8	8	8	8	8	8	8
	PBL=500 Graphite=200								
	mean	9.31	.03	2.62	6.00	.63	.06	0.00	0.00
	sd	1.25	.04	.40	1.12	.15	.05	0.00	0.00
	n	9	9	9	9	9	9	9	9
	PBL=1000 Graphite=200								
	mean	9.34	.03	2.78	6.03	.44	.09	0.00	0.00
	sd	1.11	.05	.71	.95	.17	.08	0.00	0.00
	n	10	10	10	10	10	10	10	10

TABLE 6
LUNG/BODY WEIGHT ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	LUNG/BW
Post-Exp	Control	
	mean	.63
	sd	.14
	n	10
	PBL=250 Graphite=100	
	mean	.73
	sd	.07
	n	10
	PBL=500 Graphite=100	
	mean	.82
	sd	.08
	n	10
	PBL=500 Graphite=200	
	mean	.87
	sd	.07
	n	10
	PBL=1000 Graphite=200	
	mean	.85
	sd	.05
	n	10
Post-Rec	Control	
	mean	.58
	sd	.08
	n	10
	PBL=250 Graphite=100	
	mean	.70
	sd	.06
	n	10
	PBL=500 Graphite=100	
	mean	.77
	sd	.12
	n	10
	PBL=500 Graphite=200	
	mean	.82
	sd	.08
	n	10
	PBL=1000 Graphite=200	
	mean	.84
	sd	.14
	n	10

TABLE 7
PULMONARY LAVAGE ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	TOTAL VIABLE CELLS	TOTAL CELLS	% VIABLE CELLS	% MACRO-PHAGES	% LYMPHO CYTES	% NEUTRO PHILS	% OTHER	LAVAGE FLUID PROTEIN
Post-Exp	Control								
	mean	2.24	2.26	98.64	99.70	.30	0.00	0.00	177.97
	sd	.75	.75	2.24	.67	.67	0.00	0.00	63.59
	n	10	10	10	10	10	10	10	10
	PBL=250 Graphite=100								
	mean	9.20	9.66	95.59	91.80	0.00	8.20	0.00	426.17
	sd	3.85	4.12	3.12	19.11	0.00	19.11	0.00	110.12
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=100								
	mean	8.19	8.74	93.57	92.70	0.00	7.30	0.00	483.50
	sd	1.30	1.27	3.63	16.14	0.00	16.14	0.00	143.89
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=200								
	mean	10.04	10.93	92.75	73.90	.50	25.60	0.00	523.00
	sd	2.10	2.71	4.90	22.85	1.27	22.01	0.00	88.40
	n	10	10	10	10	10	10	10	10
	PBL=1000 Graphite=200								
	mean	9.26	10.02	92.87	88.30	0.00	11.70	0.00	501.64
	sd	2.26	2.62	2.67	12.20	0.00	12.20	0.00	71.58
	n	10	10	10	10	10	10	10	10
Post-Rec	Control								
	mean	1.68	1.73	96.99	99.50	.20	.30	0.00	255.27
	sd	.48	.49	2.51	.85	.42	.67	0.00	198.39
	n	10	10	10	10	10	10	10	10
	PBL=250 Graphite=100								
	mean	7.27	7.70	94.84	77.10	0.00	22.90	0.00	463.59
	sd	1.44	1.67	2.49	10.48	0.00	10.48	0.00	173.79
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=100								
	mean	7.38	7.88	93.86	84.90	1.70	13.40	0.00	423.03
	sd	.95	1.15	2.11	13.55	5.38	12.19	0.00	106.79
	n	10	10	10	10	10	10	10	10
	PBL=500 Graphite=200								
	mean	8.24	8.81	93.68	75.20	0.00	24.80	0.00	451.09
	sd	1.96	2.19	2.31	8.47	0.00	8.47	0.00	106.52
	n	10	10	10	10	10	10	10	10
	PBL=1000 Graphite=200								
	mean	8.15	8.79	92.87	81.80	0.00	18.20	0.00	545.53
	sd	2.15	2.38	3.00	16.77	0.00	16.77	0.00	88.08
	n	10	10	10	10	10	10	10	10

TABLE 8
FOOD CONSUMPTION ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns of Recovery Animals Only by Group
Weeks 1 - 10

GROUP	FC1	FC2	FC3	FC4	FC5	FC6	FC7	FC8	FC9	FC10
Control										
mean	19.06	19.06	20.07	21.48	21.94	20.88	21.24	20.87	20.82	21.07
sd	1.57	1.49	1.52	1.77	1.57	1.61	.90	1.43	1.47	1.82
n	10	10	10	10	10	10	10	10	10	10
PBL=250 Graphite=100										
mean	18.99	18.77	20.82	21.33	22.31	20.51	21.36	21.81	21.85	20.98
sd	1.83	1.18	1.68	1.84	2.11	2.00	1.31	1.25	1.11	1.22
n	10	10	10	10	9	9	10	10	10	10
PBL=500 Graphite=100										
mean	18.58	19.04	20.97	21.01	20.88	20.56	20.05	20.97	20.86	21.45
sd	1.31	1.36	1.62	1.83	1.59	1.77	1.46	1.68	1.92	2.45
n	10	10	10	10	10	10	10	10	10	10
PBL=500 Graphite=200										
mean	19.00	18.83	20.58	21.69	22.83	20.11	20.25	21.38	21.93	20.86
sd	1.15	1.33	1.05	1.38	1.09	1.60	1.52	1.92	1.46	1.07
n	10	10	10	10	10	10	10	10	10	10
PBL=1000 Graphite=200										
mean	17.65	18.11	19.83	20.87	21.44	19.79	19.82	21.55	20.73	20.70
sd	2.58	2.10	2.23	2.39	2.05	2.46	2.27	2.16	1.58	2.39
n	10	10	10	10	10	10	10	10	10	10

TABLE 8 - Continued
FOOD CONSUMPTION ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns of Recovery Animals Only by Group
Weeks 11 - 19

GROUP	FC11	FC12	FC13	FC14	FC15	FC16	FC17	FC18	FC19
Control									
mean	20.85	19.47	19.38	18.62	19.84	19.23	20.64	20.17	19.20
sd	1.21	1.37	2.01	2.12	1.29	1.22	1.52	1.55	1.62
n	10	10	10	10	10	10	10	10	10
PBL=250 Graphite=100									
mean	20.71	20.12	21.14	20.97	22.44	22.74	23.16	22.89	22.20
sd	1.40	1.19	1.02	1.55	1.66	1.13	1.26	1.73	1.20
n	10	10	10	10	10	10	10	10	10
PBL=500 Graphite=100									
mean	21.14	20.25	19.81	20.36	21.92	23.17	22.61	22.70	21.92
sd	1.75	1.33	1.63	1.30	1.39	1.53	1.43	1.09	1.27
n	10	10	10	10	10	10	10	10	10
PBL=500 Graphite=200									
mean	21.72	20.34	21.12	21.27	23.34	24.72	23.51	22.34	23.18
sd	1.14	1.22	.95	1.31	.91	1.14	.81	1.79	.91
n	10	10	10	10	10	10	10	10	10
PBL=1000 Graphite=200									
mean	19.24	20.08	20.42	20.64	21.99	23.83	22.79	22.44	21.70
sd	1.86	1.79	2.11	1.90	2.01	1.97	1.42	1.39	1.80
n	10	10	10	10	10	10	10	10	10

TABLE 9
PULMONARY FUNCTION ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	TLC	RV	DLCO	VC	CPK	CCHORD	FVC
Post-Exp	Control							
	mean	11.74	.87	.17	10.88	1.18	.70	11.36
	sd	.91	.10	.02	.84	.12	.07	.98
	n	8	8	8	8	8	8	8
	PBL=250 Graphite=100							
	mean	10.72	.77	.16	9.95	1.05	.62	10.34
	sd	1.17	.30	.02	.95	.13	.08	.86
	n	8	8	8	8	8	8	8
	PBL=500 Graphite=100							
	mean	10.35	.63	.16	9.72	.98	.60	10.07
	sd	.43	.26	.01	.49	.05	.03	.72
	n	7	7	7	7	7	7	7
	PBL=500 Graphite=200							
	mean	9.94	.61	.14	9.34	.93	.57	9.80
	sd	.48	.23	.01	.43	.06	.03	.52
	n	8	8	8	8	8	8	8
	PBL=1000 Graphite=200							
	mean	10.23	.68	.15	9.54	.98	.59	10.15
	sd	1.44	.36	.02	1.18	.20	.07	1.12
	n	8	8	8	8	8	8	8
Post-Rec	Control							
	mean	12.05	.93	.17	11.04	1.19	.70	11.47
	sd	.89	.41	.01	.59	.11	.05	.77
	n	7	7	7	8	8	8	8
	PBL=250 Graphite=100							
	mean	11.20	1.03	.16	10.02	1.02	.62	10.33
	sd	.67	.24	.01	.63	.07	.04	.72
	n	6	6	6	8	8	8	8
	PBL=500 Graphite=100							
	mean	10.87	.68	.15	10.26	1.04	.62	10.58
	sd	.30	.26	.01	.44	.09	.05	.47
	n	6	6	6	7	7	7	7
	PBL=500 Graphite=200							
	mean	11.50	1.08	.16	10.43	1.07	.65	10.72
	sd	.98	.59	.02	.80	.11	.05	.95
	n	8	8	8	8	8	8	8
	PBL=1000 Graphite=200							
	mean	11.30	1.50	.15	9.80	.99	.62	10.12
	sd	1.38	1.18	.03	.80	.07	.06	.83
	n	7	7	7	8	8	8	8

TABLE 9 - Continued
PULMONARY FUNCTION ANALYSIS OF ANIMALS EXPOSED
TO AEROSOLS OF COMPLEX MIXTURES
Means, SDs, and Ns for Period by Group

PERIOD	GROUP	FEV50	FEV100	FEV200	FEV400	PEF	FEF75	FEF50	FEF25
Post-Exp	Control								
	mean	4.63	8.39	10.60	11.14	153.94	145.19	92.52	55.70
	sd	.55	.86	.93	.94	12.73	23.29	17.33	8.70
	n	8	8	8	8	8	8	8	8
	PBL=250 Graphite=100								
	mean	4.33	7.77	9.65	10.14	144.42	136.45	95.32	48.43
	sd	.52	.90	.87	.88	13.05	24.78	23.17	6.45
	n	8	8	8	8	8	8	8	8
	PBL=500 Graphite=100								
	mean	4.33	7.64	9.43	9.88	145.50	142.80	82.69	49.52
	sd	.33	.32	.53	.67	14.27	15.63	15.94	5.98
	n	7	7	7	7	7	7	7	7
	PBL=500 Graphite=200								
	mean	4.25	7.44	9.18	9.61	145.21	137.93	86.07	48.23
	sd	.48	.42	.42	.47	16.11	20.04	17.72	6.20
	n	8	8	8	8	8	8	8	8
	PBL=1000 Graphite=200								
	mean	4.04	7.49	9.31	9.92	138.88	127.33	88.30	51.82
	sd	.39	.50	.72	1.07	9.63	16.50	20.57	7.70
	n	8	8	8	8	8	8	8	8
Post-Rec	Control								
	mean	4.64	8.57	10.77	11.23	158.64	151.56	100.70	56.92
	sd	.37	.61	.46	.55	18.95	16.57	21.17	10.97
	n	8	8	8	8	8	8	8	8
	PBL=250 Graphite=100								
	mean	4.49	7.95	9.70	10.10	156.09	150.71	92.17	51.62
	sd	.51	.70	.80	.77	23.17	22.71	15.69	9.82
	n	8	8	8	8	8	8	8	8
	PBL=500 Graphite=100								
	mean	4.33	7.87	9.95	10.36	148.32	145.97	85.47	53.02
	sd	.30	.37	.36	.41	13.48	13.95	12.60	3.52
	n	7	7	7	7	7	7	7	7
	PBL=500 Graphite=200								
	mean	4.43	8.03	10.01	10.44	151.82	145.40	88.27	51.41
	sd	.58	.89	.86	.91	20.63	23.54	14.65	10.36
	n	8	8	8	8	8	8	8	8
	PBL=1000 Graphite=200								
	mean	4.67	8.03	9.58	9.95	155.12	154.71	102.33	56.03
	sd	.52	.55	.72	.77	20.65	20.63	21.57	8.42
	n	8	8	8	8	8	8	8	8

PART TWO

ATTACHMENT 2

LIST OF ABBREVIATIONS

ATTACHMENT 2

Abbreviations

ALBG	-	albumin (grams/deciliter serum)
ALP	-	alkaline phosphatase (international units/liter serum)
ALT	-	alanine aminotransferase (international units/liter serum)
ANOVA	-	analysis of variance
BASO	-	basophils (thousands of cells/cubic millimeter blood)
BUN	-	urea nitrogen (milligrams nitrogen/deciliter serum)
BWG	-	body weight gain in grams (body weight on indicated study day - body weight at study initiation)
CA	-	calcium (milligrams/deciliter serum)
CCHORD	-	compliance (tangent) at 0 to 10 cm H_2O (ml/cm H_2O)
CHOL	-	cholesterol (milligrams/deciliter serum)
cm	-	centimeter
CK	-	creatine kinase (international units/liter serum)
CPK	-	peak compliance (ml/cm H_2O)
CREA	-	creatinine (milligrams/deciliter serum)
DLCO	-	diffusion capacity for carbon monoxide (ml/min*torr)
EOS	-	eosinophils (thousands of cells/cubic millimeter blood)
FC	-	average daily food consumption for indicated week (grams)
FEF75	-	forced expiratory flow at 75% of remaining FVC (ml/sec)
FEF50	-	forced expiratory flow at 50% of remaining FVC (ml/sec)
FEF25	-	forced expiratory flow at 25% of remaining FVC (ml/sec)
FEV50	-	forced expiratory volume at 50 msec of expiration (ml @ 50 msec)
FEV100	-	forced expiratory volume at 100 msec of expiration (ml @ 100 msec)
FEV200	-	forced expiratory volume at 200 msec of expiration (ml @ 200 msec)
FEV400	-	forced expiratory volume at 400 msec of expiration (ml @ 400 msec)
FVC	-	forced vital capacity (ml)
GLU	-	glucose (milligrams/deciliter serum)
Graphite	-	graphite aerosol exposure concentration (mg/m^3)
HCT	-	hematocrit (percent)
HGB	-	hemoglobin (grams/deciliter blood)
IMNEU	-	immature neutrophils (thousands of cells/cubic millimeter blood)
LUNG/BW	-	lung to body weight ratio (x 100)
LYMPH	-	lymphocytes (thousands of cells/cubic millimeter blood)
MACRO	-	macrophages (percent pulmonary lavage cells counted)
MCH	-	mean corpuscular hemoglobin (picograms)
MCHC	-	mean corpuscular hemoglobin concentration (percent)
MCV	-	mean corpuscular volume (cubic microns)
MONO	-	monocytes (thousands of cells/cubic millimeter blood)
N	-	number
NEUT	-	neutrophils (thousands of cells/cubic millimeter blood)
NEUT	-	neutrophils (percent pulmonary lavage cells counted)
NRBC	-	nucleated red blood cells (thousands of cells/cubic - millimeter blood)
OTHER	-	cells other than macrophages, lymphocytes, neutrophils (percent pulmonary lavage cells counted)
PBL	-	petroleum-based liquid (fog oil) exposure concentration (mg/m^3)
PEF	-	peak expiratory flow (ml/sec)
PHOS	-	inorganic phosphate (milligrams phosphate/deciliter serum)

PLT	-	platelet count (thousands of cells/cubic millimeter blood)
Post-Exp	-	post-exposure
Post-Rec	-	post-recovery
PROTEIN	-	lavage fluid protein (micrograms/milliliter)
RBC	-	red blood cell count (millions of cells/cubic millimeter blood)
RV	-	residual volume (ml)
SD	-	standard deviation
SDH	-	sorbitol dehydrogenase (international units/liter serum)
TBA	-	total bile acids (micromoles/liter serum)
TLC	-	total lung capacity (ml)
TP	-	total protein (grams protein/deciliter serum)
TRIG	-	triglycerides (milligrams/deciliter serum)
VC	-	vital capacity (ml)
WBC	-	white blood cell count (thousands of cells/cubic millimeter blood)

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